KINETICS OF CHEMICAL REACTIONS IN ADIABATIC SYSTEMS

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Summary

The kinetics of first- and second-order reactions in adiabatic systems are discussed and a solution of the differential equations is given.

I. Introduction

In the study of the kinetics of chemical reactions the isothermicity of the reaction system is usually supposedly achieved by keeping the temperature of the thermostat containing the reaction vessel constant. However, the enthalpy change, which accompanies the reaction, may be large enough to change the temperature of the reacting volume appreciably from that of the thermostat and because of the profound influence of temperature on reaction velocity this could clearly be a source of error. An example, taken from the many publications where this would seem to occur, is that of Barb *et al.* (1951), whose data (see Table 1, p. 599) on the rate constants obtained with small and large volumes show differences of up to 30 per cent.

The special case of reaction under adiabatic conditions allows the explicit solution of the differential equations of the kinetics and, as far as the author is aware, such calculations have not been published. Certain cases of non-isothermal systems, in which the temperature of the system was determined by the external conditions, are discussed by Sherman (1936) and Gaensslen and McKenzie (1955).

II. Theory

Consider a reaction starting at temperature T_0, and reaching a final temperature T_f, after the reaction has taken place. As the system is assumed to be thermally insulated from its surroundings, the instantaneous value of the temperature is determined by the amounts of the substances reacted. In other words, the temperature in the reacting system and the instantaneous concentrations of the substances are mutually dependent. The final value of the temperature T_f of the system is a function of the enthalpy of the reaction ΔH, of the original concentration c_0 of the reacting substance(s), and of the heat capacity C_p of the system. If we consider only cases where the temperature change $T_f - T_0$ is not too great, the simplifying assumption that the enthalpy of the reaction is independent of temperature and concentration is justified. The same applies to the heat content of the system and to the Arrhenius energy of activation. We also assume that any changes in concentration of the solution due to the volume change of reaction are negligible.

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It is easily verified that the functional connection between c_0, c, T_0, T, C_p, and ΔH is given by

$$c=c_0+\frac{C_p(T-T_0)}{\Delta H}=-\frac{C_p(T_f-T)}{\Delta H}, \quad \ldots\ldots\ldots \quad (1)$$

and therefore,

$$\mathrm{d}c=\frac{C_p}{\Delta H}\mathrm{d}T. \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

We propose to discuss only two cases: first-order reaction described kinetically by

$$-\mathrm{d}c=kc\mathrm{d}t, \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

and a second-order reaction, described by

$$-\mathrm{d}c=kc^2\mathrm{d}t. \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (3a)$$

Substituting (**1**) and (**2**) in (**3**) and (**3a**) we have, after rearrangement,

$$\mathrm{d}T=-k\left[\frac{\Delta Hc_0}{C_p}+(T-T_0)\right]\mathrm{d}t=k(T_f-T)\mathrm{d}t, \quad \ldots\ldots\ldots\ldots \quad (4)$$

and

$$\mathrm{d}T=-k\frac{C_p}{\Delta H}\left[\frac{\Delta Hc_0}{C_p}+(T-T_0)\right]^2\mathrm{d}t=-k\frac{C_p}{\Delta H}(T_f-T)^2\mathrm{d}t. \quad \ldots \quad (4a)$$

For simplicity let us assume that the rate constant is given by

$$k=Z\exp(-E/RT), \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

where Z is independent of the temperature. Then

$$\int_0^t \mathrm{d}t=t=\frac{1}{Z}\int_{T_0}^{T}\frac{\exp(E/RT)}{T_f-T}\mathrm{d}T, \quad \ldots\ldots\ldots\ldots \quad (6)$$

and

$$\int_0^t \mathrm{d}t=t=-\frac{\Delta H}{C_pZ}\int_{T_0}^{T}\frac{\exp(E/RT)}{(T_f-T)^2}\mathrm{d}T. \quad \ldots\ldots\ldots \quad (6a)$$

The integrals on the right-hand side of (**6**) and (**6a**) may be rearranged as

$$t=\frac{1}{Z}\int_{u_0}^{u}\frac{\mathrm{e}^u}{u}\mathrm{d}u-\frac{1}{k_f}\int_{\omega_0}^{\omega}\frac{\mathrm{e}^\omega}{\omega}\mathrm{d}\omega, \quad \ldots\ldots\ldots\ldots\ldots \quad (7)$$

and

$$t=-\frac{\Delta H}{C_pk_f}\frac{E}{RT_f^2}\left\{\frac{\mathrm{e}^\omega}{\omega}-\frac{\mathrm{e}^{\omega_0}}{\omega_0}-\int_{\omega_0}^{\omega}\frac{\mathrm{e}^\omega}{\omega}\mathrm{d}\omega\right\}, \quad \ldots\ldots\ldots \quad (7a)$$

where $u_0=E/RT_0$, the variable $u=E/RT$, the value of $\omega_0=(E/RT_f)(T_f/T_0-1)$, and the variable $\omega=(E/RT)(T_f/T-1)$, k_f is the value of the rate constant at the final temperature T_f as given by equation (**5**). The last integrals in (**7**) and (**7a**) can be taken from the tables of exponential integrals as $\mathrm{Ei}(\omega)-\mathrm{Ei}(\omega_0)$ and the

first integral in (7) calculated for our case by the approximate formula of exponential integrals for large values of the argument, taking thereby only the members with u^0 and u^{-1},

$$\int \frac{e^u}{u} du = \frac{e^u}{u}\left(1 + \frac{1!}{u} + \frac{2!}{u^2} + \frac{3!}{u^3} + \ldots\right).$$

III. Application

To illustrate the results expressed by (7) and (7a) the following numerical values were assumed :

$-\Delta H = 20{,}000$ cal mole^{-1},
$T_0 = 300$ °K,
$c_0 = 1$ mole l^{-1},
$C_p = 1000$ cal l^{-1} degree^{-1},
$E/R = 10{,}000$ degrees,
$k_0 = 2 \cdot 3026 \times 10^{-2}$ min^{-1} for the first order,
and $k_0 = 2 \cdot 3026 \times 10^{-2}$ l mole^{-1} min^{-1} for the second-order reaction.

With these values, $T_f = 320$ °K, $u_0 = 33 \cdot 3333$, and $u_f = 31 \cdot 2500$; while $\omega_0 = 2 \cdot 0833$ and $\omega_f = 0$.

Table 1

Concentration-time (min) relationship

Concentration (mole l^{-1})	First-Order Reaction		Second-Order Reaction	
	Isothermal	Adiabatic (from (9))	Isothermal	Adiabatic (from (9a))
0·9	4·58	4·10	4·83	4·31
0·8	9·69	7·78	10·86	8·64
0·7	15·49	11·13	18·61	13·12
0·6	22·19	14·27	28·95	17·95
0·5	30·10	17·26	43·43	23·41
0·4	39·79	20·24	65·14	30·05
0·3	52·29	23·36	101·34	39·04
0·2	69·90	26·94	173·72	53·67
0·1	100·00	31·93	390·86	89·26

It will be observed that the concentration-time curves are S-shaped, showing that the rate v of the reaction increases with time and passes through a maximum. For the maximum value $dv/dt = dv/dT = 0$ must be satisfied, and this condition yields from (4) and (4a) for the temperature T_v at which the rate of the reaction is a maximum

$$T_v = -\frac{E}{2R} + \frac{E}{2R}\left(1 + \frac{4RT_f}{E}\right)^{\frac{1}{2}}, \quad \ldots\ldots\ldots\ldots \quad (8)$$

and

$$T_v = -\frac{E}{4R} + \frac{E}{4R}\left(1 + \frac{8RT_f}{E}\right)^{\frac{1}{2}}. \quad \ldots\ldots\ldots\ldots \quad (8a)$$

With the assumed data used in calculating the values of Table 1 the concentration showing the maximum velocity is 0·48 mole l^{-1} for the first-order, and 0·91 mole l^{-1} for the second-order reaction.

IV. Non-Adiabatic Systems

In actual practice, the reaction system is not adiabatic and there is a flow of heat between the reaction volume and the thermostat. If we assume that the temperature in the reaction volume is kept uniform by stirring and that the heat transfer is proportional to the temperature difference between the reaction flask and the thermostat, equations (**1**) and (**2**) change to

$$c = c_0 + \frac{C_p(T - T_0)}{\Delta H} + \frac{S}{\Delta H}\int_0^t (T - T_0)\mathrm{d}t, \quad \ldots\ldots\ldots \quad (\mathbf{9})$$

and

$$\mathrm{d}c = \frac{C_p}{\Delta H}\mathrm{d}T + \frac{S}{\Delta H}(T - T_0)\mathrm{d}t, \quad \ldots\ldots\ldots\ldots\ldots \quad (\mathbf{10})$$

and (**4**) with (**4a**) to

$$\mathrm{d}T = -k\left[\frac{\Delta H c_0}{C_p} + (T - T_0) + \frac{S}{C_p}\int_0^t (T - T_0)\mathrm{d}t\right]\mathrm{d}t - \frac{S}{C_p}(T - T_0)\mathrm{d}t, \quad \ldots\ldots (\mathbf{11})$$

and

$$\mathrm{d}T = -\frac{kC_p}{\Delta H}\left[\frac{\Delta H c_0}{C_p} + (T - T_0) + \frac{S}{C_p}\int_0^t (T - T_0)\mathrm{d}t\right]^2\mathrm{d}t - \frac{S}{C_p}(T - T_0)\mathrm{d}t, \quad .. \quad (\mathbf{11a})$$

where S stands for the overall coefficient of heat transfer between the reaction volume and the thermostat.

Equations (**11**) and (**11a**) may be solved by numerical methods. The temperature of the solution rises to a maximum and after sufficient time towards the end of the reaction acquires the temperature of the thermostat. There is no longer a unique relation between the concentrations of the reacting substances and the temperature of the system. Therefore the temperature has to be found from (**11**) and (**11a**) as a function of time and the corresponding concentration thereafter from (**9**).

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SECOND-ORDER REACTION AND DIFFUSION IN POLAROGRAPHIC ANALYSIS

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Summary

The diffusion and second-order reaction have been discussed and a formula found for the current flowing to the electrode.

I. Introduction

A spherical electrode is placed in a solution of substance A which originally has a concentration $[A_0]$. Substance A diffuses to the electrode and there picks up an electron e to become substance B, which now diffuses away from the electrode. Two atoms of substance B now react to form one atom of A and one atom of an inert substance C. The quantity measured in the experiment is the current flowing to the electrode, expressed as

$$i = n.F.S.D_1.\left(\frac{\mathrm{d}[A]}{\mathrm{d}r}\right)_{r=r_0} \qquad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

(Kolthoff and Lingane 1941), where r is the distance from the centre of the electrode, r_0 is its radius, S is its surface area, n and F are the number of electrons transferred and the Faraday respectively, and D_1 is the diffusion coefficient.

Our problem is to determine i in terms of various chemical constants.

II. Mathematical Formulation of the Problem

The chemical equations to be resolved are

$$\begin{aligned} &A + e \rightarrow B\,; \\ &B + B \rightarrow A + C\,; \end{aligned}$$

we consider only the second process, which is equivalent to the following mathematical equations:

(*a*) *For the Diffusion*

$$\left.\begin{aligned} \frac{\partial[A]}{\partial t} &= D_1 \cdot \nabla^2[A], \\ \frac{\partial[B]}{\partial t} &= D_2 \cdot \nabla^2[B], \\ \frac{\partial[C]}{\partial t} &= D_3 \cdot \nabla^2[C], \end{aligned}\right\} \qquad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

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(Margenau and Murphy 1943), where D_1, D_2, D_3 are diffusion constants and [A], [B], [C] are concentrations of various substances.

(b) For the Reaction

$$\left.\begin{aligned}\frac{\partial[\mathrm{B}]}{\partial t}&=-k[\mathrm{B}]^2,\\ \frac{\partial[\mathrm{A}]}{\partial t}&=\tfrac{1}{2}k[\mathrm{B}]^2,\\ \frac{\partial[\mathrm{C}]}{\partial t}&=\tfrac{1}{2}k[\mathrm{B}]^2,\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots (3)$$

where k is the velocity constant of the reaction.

Combining (**2**) and (**3**), we obtain for diffusion and reaction the following equations :

$$\left.\begin{aligned}\frac{\partial[\mathrm{A}]}{\partial t}&=D_1\cdot\nabla^2[\mathrm{A}]+\tfrac{1}{2}k[\mathrm{B}]^2,\\ \frac{\partial[\mathrm{B}]}{\partial t}&=D_2\cdot\nabla^2[\mathrm{B}]-k[\mathrm{B}]^2,\\ \frac{\partial[\mathrm{C}]}{\partial t}&=D_3\cdot\nabla^2[\mathrm{C}]+\tfrac{1}{2}k[\mathrm{B}]^2.\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots (4)$$

For a steady state, in which we are interested,

$$\frac{\partial[\mathrm{A}]}{\partial t}=\frac{\partial[\mathrm{B}]}{\partial t}=\frac{\partial[\mathrm{C}]}{\partial t}=0,$$

and equations (**4**) become

$$\left.\begin{aligned}\nabla^2[\mathrm{A}]+k_1[\mathrm{B}]^2&=0,\\ \nabla^2[\mathrm{B}]-k_2[\mathrm{B}]^2&=0,\\ \nabla^2[\mathrm{C}]+k_3[\mathrm{B}]^2&=0,\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots (5)$$

where

$$\left.\begin{aligned}k_1&=k/2D_1\,;\\ k_2&=k/\mathrm{D}_2\,;\\ k_3&=k/2D_3.\end{aligned}\right\} \quad \ldots\ldots\ldots\ldots\ldots (6)$$

Taking the electrode as a sphere of radius r_0 and a solution of infinite extent, we have the following boundary conditions :

(i) when $r=r_0$, $\quad [\mathrm{A}]=0, \quad [\mathrm{B}]+[\mathrm{C}]=[\mathrm{A}_0]$;
(ii) when $r\to\infty$, $\quad [\mathrm{A}]\to[\mathrm{A}_0], \ [\mathrm{B}]=[\mathrm{C}]\to 0$.

III. Solution of $\nabla^2[\mathrm{B}]-k_2[\mathrm{B}]^2=0$

Since the electrode is spherical, the solutions of the differential equations will be spherically symmetrical. Thus the equation

$$\nabla^2[\mathrm{B}]-k_2[\mathrm{B}]^2=0$$

becomes

$$\frac{\mathrm{d}^2[\mathrm{B}]}{\mathrm{d}r^2}+\frac{2}{r}\frac{\mathrm{d}[\mathrm{B}]}{\mathrm{d}r}=k_2[\mathrm{B}]^2. \quad \ldots\ldots\ldots\ldots\ldots (7)$$

Putting

$$t=\sqrt{(k_2)}r, \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (8)$$

we obtain

$$[\mathrm{B}]''(t)+\frac{2}{t}[\mathrm{B}]'(t)=[\mathrm{B}]^2(t), \quad \ldots\ldots\ldots\ldots\ldots \quad (9)$$

dashes indicating differentiation with respect to t. This equation is closely connected with the Lane-Emden differential equation and was thoroughly investigated by Fowler (1931*a*, 1931*b*), who has shown that, as $t\to\infty$,

$$[\mathrm{B}]\sim 2/t^2. \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (10)$$

This asymptotic behaviour of $[\mathrm{B}(t)]$ suggests the form

$$[\mathrm{B}(t)]=\frac{2}{t^2}\varphi(t), \quad \ldots\ldots\ldots\ldots\ldots \quad (11)$$

where $\varphi(t)\to 1$, as $t\to\infty$.

We find from (9) and (11) that $\varphi(t)$ then satisfies the following differential equation :

$$t^2\cdot\varphi''(t)-2t\cdot\varphi'(t)+2\varphi(t)=2\varphi^2(t). \quad \ldots\ldots\ldots \quad (12)$$

Assuming now that

$$\varphi(t)=\sum_{j=0}^{\infty} a_j t^{-jn}, \quad \ldots\ldots\ldots\ldots\ldots \quad (13)$$

where n is some positive constant we find from (12), by comparing coefficients of equal powers of t, that

$$n^2+3n-2=0, \quad \ldots\ldots\ldots\ldots\ldots \quad (14)$$

or

$$n=\tfrac{1}{2}(-3+\sqrt{17})=0\cdot 5615528, \quad \ldots\ldots\ldots\ldots \quad (15)$$

and that the coefficients a_j are given by the recurrence formula

$$a_j=\frac{2\sum_{i=1}^{j-1} a_i a_{j-i}}{j^2(2-3n)+(3nj-2)}, \quad \ldots\ldots\ldots\ldots \quad (16)$$

where $j>2$, also

$$a_0=1, \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (17)$$

and a_1 is indeterminate, say a.

These coefficients a_j can then be expressed in the form

$$a_j=\gamma_j a^j \qquad j=0,\ 1,\ \ldots, \quad \ldots\ldots\ldots\ldots \quad (18)$$

where γ_j are functions of j and n only ; the following are the first 10 values :

$$\left.\begin{array}{ll} \gamma_0=1, & \gamma_1=1, \\ \gamma_2=0\cdot 760259, & \gamma_3=0\cdot 516125, \\ \gamma_4=0\cdot 329155, & \gamma_5=0\cdot 201734, \\ \gamma_6=0\cdot 120280, & \gamma_7=0\cdot 070279, \\ \gamma_8=0\cdot 040426, & \gamma_9=0\cdot 022978. \end{array}\right\} \quad \ldots\ldots\ldots \quad (18a)$$

Thus

$$\varphi(t)=\sum_{j=0}^{\infty} a^j\gamma_j t^{-jn}, \quad \ldots\ldots\ldots\ldots\ldots (19)$$

or, combining (19) with (11) and (8)

$$[\mathrm{B}(r)]=2/k_2r^2\sum_{j=0}^{\infty} a^j\gamma_j\{\sqrt{(k_2)}r\}^{-jn}, \quad \ldots\ldots\ldots (20)$$

where a is still indeterminate.

IV. Solution of $\nabla^2[\mathrm{A}]+k_1[\mathrm{B}]^2=0$

Due to spherical symmetry we have

$$[\mathrm{A}]''(r)+\frac{2}{r}[\mathrm{A}]'(r)=-k_1[\mathrm{B}]^2(r), \quad \ldots\ldots\ldots (21)$$

which on putting

$$s=\sqrt{(k_1)}r \quad \ldots\ldots\ldots\ldots\ldots\ldots (22)$$

becomes

$$[\mathrm{A}]''(s)+\frac{2}{s}[\mathrm{A}]'(s)=-[\mathrm{B}]^2(s). \quad \ldots\ldots\ldots\ldots (23)$$

In view of the boundary condition (ii) we now assume that

$$[\mathrm{A}(s)]=[\mathrm{A}_0]-\frac{1}{s^2}\psi(s), \quad \ldots\ldots\ldots\ldots (24)$$

where $\psi(s)$ *is finite as* $s\to\infty$. This function $\psi(s)$ then satisfies the differential equation

$$s^2\cdot\psi''-2s\cdot\psi'+2\psi=\varphi^2(s), \quad \ldots\ldots\ldots\ldots\ldots (25)$$

or

$$s^2\cdot\psi''-2s\cdot\psi'+2\psi=\sum_{j=0}^{\infty}\left(\sum_{i=0}^{j} b_ib_{j-i}\right)s^{-nj}, \quad \ldots\ldots\ldots (26)$$

where

$$b_j=K^{nj}a_j, \quad \ldots\ldots\ldots\ldots\ldots\ldots (27)$$

and

$$K=\sqrt{(k_1/k_2)}. \quad \ldots\ldots\ldots\ldots\ldots\ldots (28)$$

If now

$$\psi(s)=\sum_{j=0}^{\infty} c_js^{-nj}, \quad \ldots\ldots\ldots\ldots\ldots\ldots (29)$$

we find from (26), by comparing coefficients of equal powers of s, that

$$c_j=a^j\delta_j, \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (30)$$

where

$$\delta_j=\frac{K^{nj}\sum_{i=0}^{j}\gamma_i\gamma_{j-i}}{j^2(2-3n)+(3nj+2)}. \quad \ldots\ldots\ldots\ldots (31)$$

Thus

$$[A(s)]=A_0-\sum_{j=0}^{\infty} a^j\delta_j s^{-(2+nj)},^* \quad \ldots\ldots\ldots\ldots \quad (32)$$

and

$$[A(r)]=A_0-\sum_{j=0}^{\infty} a^j\varepsilon_j r^{-(2+nj)}, \quad \ldots\ldots\ldots\ldots \quad (33)$$

the coefficients ε_j being defined by the equation

$$\varepsilon_j=\delta_j/[K_1]^{\frac{1}{2}(2+nj)}. \quad \ldots\ldots\ldots\ldots\ldots \quad (34)$$

The constant a can now be determined from the equation (33). For $r=r_0$, [A] is zero. If we take, for simplicity's sake, the radius r_0 as unity, that is,

$$r_0=1, \quad \ldots\ldots\ldots\ldots\ldots \quad (35)$$

then

$$[A_0]-\sum_{j=0}^{\infty} \varepsilon_j a^j=0. \quad \ldots\ldots\ldots\ldots\ldots \quad (36)$$

From this equation a can be evaluated numerically to any required degree of accuracy.

V. Determination of the Current i

From (33)

$$\frac{d[A]}{dr}=\sum_{j=0}^{\infty} \varepsilon_j a^j(2+nj)r^{-(3+nj)}, \quad \ldots\ldots\ldots\ldots \quad (37)$$

and, hence, by (1) and (35)

$$i=n.F.S.D_1.\sum_{j=0}^{\infty} (2+nj)\varepsilon_j a^j. \quad \ldots\ldots\ldots\ldots\ldots \quad (38)$$

VI. Conclusion

The following is the suggested order of calculations necessary for determination of i: (i) Determine $K=\sqrt{(k_1/k_2)}=\sqrt{(D_2/2D_1)}$; (ii) using (18a) and (31) determine δ_j; (iii) using (34) determine ε_j; (iv) using (36) numerically evaluate the constant a; (v) use (38) for the calculation of the current i.

VII. Acknowledgments

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* In solving equation (26) we consider only the particular integral since for $\psi(s)$ to be finite as $s\to\infty$ the complementary function must vanish.

THE RECORDING OF D.C. POLAROGRAPHIC WAVES AND THE MEASUREMENT OF THE INSTANTANEOUS CURRENT AT THE END OF THE LIFE OF THE MERCURY DROP

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Summary

Because of the slowness of response of the current detectors used in the infancy of polarography, it has become the custom to measure the average current rather than the instantaneous current at some given time near the end of the life of the mercury drop. McKenzie (1958*a*) has pointed out that there are a number of theoretical advantages to be gained by measurement of instantaneous diffusion current. The work reported in the present paper shows that this measurement can be made accurately with conventional electronic equipment. Owing to the inherent lag in automatic recording polarographs which measure average current, it is not possible to obtain from the records the half-wave potential and slope with good accuracy. It is shown that the advantages of automatic recording and accuracy in determining the half-wave potential and slope may be realized by recording instantaneous current-voltage curves. Also abnormalities in current-time curves may be readily detected. Apparatus using a conventional recorder and a preamplifier which is a modification of that of Kelley and Miller (1952) is described. A device which can be used to control pen drive is also described.

I. Introduction

The accurate measurement of the characteristics of the polarographic wave, i.e. diffusion current, slope, and half-wave potential, is of prime importance in analytical and physicochemical applications of polarography. The simplest of the circuits for determining polarographic waves manually was introduced by Heyrovsky (1922). With the dropping mercury electrode the current at each value of the applied e.m.f. is not constant, but oscillates as each mercury drop grows and falls. Because of the slowness of response of the galvanometers available for measuring current in the early days of polarography, it became the custom to measure the average current during the life of the mercury drop, rather than the instantaneous current at some given time in drop life. As long as polarizing voltage was held steady during the determination of each point on the current-voltage curve, it was possible to obtain accurate measurements of the characteristic values. This point-by-point determination of the current-voltage curve is referred to as the manual method.

Routine measurements became more convenient with the introduction of an automatic recording polarograph by Heyrovsky and Shikata (1925). Instead

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of the polarizing voltage being changed manually in steps, automatic recording of the current-time curve was achieved by using a motor to drive the slidewire, and the corresponding current through the polarographic cell was photographically recorded with a sensitive d'Arsonval galvanometer. Numerous modifications of this instrument have been developed (see, for example, Kolthoff and Lingane 1952). Since the galvanometers in them are usually heavily damped and the polarizing potentiometers are of limited accuracy, the records obtained are not suitable for accurate determination of half-wave potential and wave slope.

The availability of pen recorders of the self-balancing potentiometer type made it possible to develop recording polarographs which were more convenient to use. The first commercial instrument of this type was the Leeds and Northrup Electrochemograph which was designed to balance the average current through the polarographic cell. The disadvantages of this type of instrument, where the response is slow and the series resistance large, have been discussed by the present authors (McKenzie and Taylor 1948) elsewhere. Lingane (1946) has discussed the unsatisfactory characteristics of the Sargent polarograph, which uses a heavily damped Brown Electronik recorder.

Blomgren (1949) developed a polarograph in which the average current was recorded on a Speedomax G recorder after amplification with a D.C. amplifier employing the principle of negative feedback to ensure linearity. Kelley and Miller (1952) described a polarograph using a preamplifier with a Brown Electronik recorder. This was provided with a linear compensator to minimize the effect of condenser current on the recorded polarograms and also a " curve follower " for automatically subtracting the residual current curves at high sensitivities.

All the above polarographs using electronic recorders were designed to measure the average current during the life of the mercury drop. When a steady polarizing voltage is applied, as in the manual method, the oscillations persist to some extent and the average current has been arbitrarily taken as the average of the recorder oscillations. The true average depends on the shape of the wave-form and the above procedure may not give a good approximation unless the oscillations are very small. Further, when the current is sufficiently smoothed for this purpose, the speed of response to a changing polarizing voltage is reduced so that accurate automatic recording of a current-voltage wave is not possible. Most workers seem to have failed to take advantage of the fact that the response of many of the continuous balance electronic recorders is fast enough to give an accurate measurement of the current in the latter part of the drop life. The half-wave potential and wave slope may be found accurately from an automatic recording of this type, whereas it is difficult to make a satisfactory estimate of errors when average current is recorded.

Schulman, Battey, and Jelatis (1947) were probably the first to realize some of the advantages of measurement of peak current. They used an Esterline-Angus recorder, giving a full-scale deflection in 0·5 sec. The recorder follows the growth of current during the life of the drop with reasonable accuracy. The application of this instrument is limited by its narrow chart and non-rectilinear coordinate system. In 1950, the Leeds and Northrup Company

developed their Electrochemograph Type E. This instrument uses a Speedomax Microampere recorder (1 sec). It is inherently capable of recording the maximum current (Leeds and Northrup 1950), but has generally been used to measure "average" current.

In the study of instantaneous current-time curves reported in the preceding communication (McKenzie 1958*a*) it was pointed out that there are a number of advantages in measurement of instantaneous current near the end of drop life rather than the average current. In the present paper the authors have assessed the accuracy with which instantaneous current at the end of drop life can be measured with conventional electronic recorders. At the same time a study has been made of the automatic recording of instantaneous current-voltage curves.

As indicated above, the slow speed of response of the current-detecting system in automatic polarographs that measure average current causes a considerable lag in the recording of the rising part of the polarographic wave (McKenzie 1958*c*, Fig. 4). As the rate of change of potential increases, the error in half-wave potential and slope becomes greater. A new problem appears when recording instantaneous current with recorders of rapid response. If a high rate of change of the applied e.m.f. (greater than about 600 mV/min) is used, a peak will occur at the crest of the wave prior to the limiting diffusion region (McKenzie 1958*c*, Fig. 5). This was noted without comment by Schulman, Battey, and Jelatis (1947). However, the effect is reproducible and the peak observed is analogous to that obtained in mercury pool polarographic scanning (cf. Streuli and Cooke 1953). The peak current can be predicted from the Randles and Sevcik equations (Streuli and Cooke 1953). At low scanning rates (less than 400 mV/min) the peak disappears (McKenzie 1958*c*, Fig. 5). Even with slower scanning the question remains as to whether the current is greater at a given applied potential on the rising part of the wave than it would be if the same voltage were applied manually. In the present work it has been found that this is in fact the case. However, at low scanning rates the effect is small.

As a result of considerations such as the above, together with response characteristics of available recorders, it was decided to use a scanning rate of 100 mV/min since it was desired to record half-wave potential and slope accurately in the present work. A rate of 200 mV/min may be used for analytical purposes if desired.

II. Experimental

(*a*) *Materials and Methods*

The materials and general polarographic procedure were similar to those described in McKenzie's (1958*a*) paper.

(*b*) *Apparatus*

The recorder used for most of the present measurements was a Brown Electronik recorder, manufactured by the Minneapolis-Honeywell Regulator Co., Philadelphia, Pa. It had a slidewire span of 2·5 mV and 4 sec pen speed. The amplifier was modified according to the general scheme adopted by Kelley and Miller (1952) with some further modifications which are described below.

A schematic diagram is shown in Figure 1. Although it was possible to use current ranges from 100 down to 0·05 μA full scale, the ranges below 0·2 μA full scale are not very useful unless means are provided for compensating for residual capacity currents. This was not done for the present series of experiments.

The input circuit was arranged to give quick response to changes in current during drop growth, so that the aim of recording instantaneous current near the end of drop life could be realized. This requirement meant that interference due to stray pick up was likely to be more severe. The A.C. mains at 50 c/s and transients from the power supply were the main sources of interfering currents. These were brought to a satisfactory level by shielding and careful

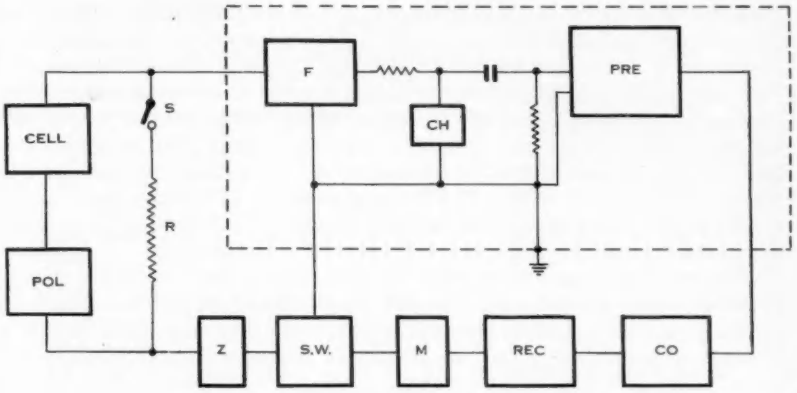

Fig. 1.—Electronic schematic diagram.

Cell, Polarographic cell ; *Pol*, polarizer ; *R*, measuring resistor ; *S*, switch for selecting measuring resistor ; *Z*, Helipot circuit for zero-setting ; *SW*, slidewire ; *F*, twin-T filter to reject 50 c/s ; *Ch*, chopper with isolated drive coil ; *Pre*, preamplifier, 12AU7 and 12AX7 in cascade ; *Co*, control of pen drive, 6AU6+6AU6 in phase-sensitive arrangement ; *Rec*, recorder with first valve removed ; *M*, balancing motor.

wiring in the measuring circuits to avoid loops and by the inclusion of a twin-T filter (Kelley and Fisher 1956) between the measuring circuits and the input to the amplifier. The filter which gave minimum transmission introduced a resistance at 50 c/s of 600,000 Ω in series with the input, and this was followed by a further resistance of 1 MΩ to minimize the loading effect of the chopper. A low resistance (25 Ω) 10-turn helical potentiometer (Beckman Helipot Bulletin 104A) in series with the recorder slidewire gave a means of setting zero anywhere on the recorder chart and compensated for steady stray current. To reduce the level of interfering currents in a high impedance circuit, it is necessary to keep the circuit for the driving coil of the chopper well away from the connections to the contacts. It was found easier to do this with a chopper, Model A–11, made by Stevens-Arnold Inc., Boston, Mass., than with a modified Brown chopper as used by Kelley and Miller (1952).

The preamplifier was very similar to that used by Kelley and Miller except the triode in the fourth stage was arranged as a band-pass filter for 50 c/s by connecting a twin-T filter between the plate and grid (Minneapolis-Honeywell 1950). This was found desirable to reduce the effect of transient disturbances. The preamplifier was followed by a stage which gave separate control over the rate of pen travel in the up-scale and down-scale directions. Two pentodes were connected in a circuit similar to the power stage of the main amplifier which drives the motor (Minneapolis-Honeywell 1950) except the plate current was held near zero when there was no signal voltage, and the screens were supplied by regulated D.C. (Pentodes give a better wave-form than triodes in this circuit arrangement.) By connecting the input grids separately to potentiometers across the output of the preamplifier it was possible to adjust the gain according to the relative phase of the signal. Maximum permissible gain could be used on the pentode which was in action when the current was increasing during drop growth. The input to the other pentode was reduced so that when the drop fell off, the pen would be driven very slowly from the maximum value. This setting, together with correct damping of the motor, ensured that a satisfactory indication of the maximum current was given on the recorder chart. This feature is purely optional and is only used if several polarograms are to be recorded on the same chart. The limited excursions of the pen motor enable this to be done more easily. It was not necessary to use this control to obtain the results reported in this paper, as it was shown that the response of the 4-sec recorder was fast enough to measure the maximum current even when full pen excursions were allowed. Wåhlin and Bresle (1956) limited pen travel by switching on the balancing motor only at chosen intervals during drop life. Although their method allows the current to be measured at any convenient stage of drop growth, it may be difficult to bring some balancing motors to rest quickly enough when the power is switched off in the way described.

The output of the control stage was taken from a resistor connected between the centre tap of the power transformer supplying the plates of the pentodes and the cathode returns. The connections to the main amplifier of the recorder were similar to those described by Kelley and Miller.

An alternative input circuit was used when it was desired to measure the average current during drop life for a given fixed applied voltage. The potential difference across the measuring resistor charged a capacitor of 50 μF through a resistor of 200,000 Ω so that the potential difference across the capacitor instead of the potential difference across the measuring resistor appeared at the input terminals. Oscillations of the pen during drop life were reduced to two divisions (peak to peak) by this arrangement. Since this work was done, Kelley and Fisher (1956) have developed a better method using a quadruple parallel-T RC filter. It is only applicable to instruments with high impedance input such as the present one and that of Kelley and Miller (1952).

The polarizing unit employed was simple in design and sufficiently versatile for most purposes. It was of low resistance and accurate to ±1 mV, both of which features are important in the present work. Calibration was effected against a standard cell using a Cambridge Pot galvanometer (Cambridge Instru-

ment List 163) as null-meter. The initial potential was selected manually in the range 0 to 2·5 V, or 0 to −2·5 V. The increasing potential was provided by a motor-driven Helipot potentiometer connected in series with the manual potentiometer. The calibrated 10-turn Helipot potentiometer had a span of 1000 mV and was of low resistance and low temperature coefficient. It was driven by a synchronous motor, usually at a rate of 100 mV/min.

III. Results

In Table 1 results are presented for the measurement of limiting diffusion current (corrected for residual current) for various solutions. Column 3 lists the maximum limiting diffusion current, that is, the current at the end of the drop life, measured with the recording polarograph using the modified Brown recorder. Considering the nature of the diffusion current-time curves observed

Table 1

Measurement of diffusion current at 25 °C

Solution	No. of Measurements	Max. Current		Av. Current RC Filter		Av. Current Galvanometer		$i_{max.}/i_{av.}$	
		Mean	S*	Mean	S	Mean	S	Expt.	Oscillograph
0·002M Cd(II) in 1M KCl No suppressor	4	15·98	0·10	12·83	0·07	12·91	0·08	1·24	1·24
0·002M Cd(II) in 1M KCl 0·01 g/100 ml Gelatin	4	15·83	0·03	12·78	0·05	12·83	0·05	1·24	1·24
0·002M Pb(II) in 1M KCl 0·01 g/100 ml Gelatin	6	17·78	0·05	14·14	0·07	14·17	0·03	1·26	1·27
0·002M Tl(I) in 0·1M KCl 0·01 g/100 ml Gelatin	4	12·45	0·04	9·67	0·03	9·74	0·02	1·28	1·29

* Where S^2 is $\Sigma d^2/n-1$.

by McKenzie (1958*a*) and the response characteristics of the recorder, the polarograph should accurately record the instantaneous current during the later stages of drop life. Nevertheless it is obviously desirable to make a comparison with measurements obtained with an oscillographic recorder. On account of the limited precision (*c.* 2 per cent.) of most oscillographic recorders it is difficult to make this comparison with high accuracy. Somewhat greater precision can be obtained with the oscillographic recorder by measuring the ratio of the maximum current to the integrated average current. Therefore, a comparison has been made of this ratio, rather than of maximum current.

In column 4 the average current measured on the Brown recorder using the RC filter is given. The average current was also determined on a manual polarograph by measuring the deflection of a calibrated galvanometer in series with the polarographic cell. The Tinsley galvanometer used was heavily damped by means of a parallel resistance so that its half-period was of the order of 20 sec. These results are listed in column 5. In both cases the average current was taken as the average of the oscillations and it can be seen that both methods agree within 0·7 per cent. for this measurement. It has been shown by Taylor, Smith, and Cooter (1949) that the average of the oscillations for the heavily damped galvanometer agrees within $\pm 0{\cdot}5$ per cent. of the integrated (true) average current. The ratio of the maximum to the average current is given in column 6.

For comparison, the ratio of the maximum current to the integrated average current, determined oscillographically, is given in column 7. These figures are those of McKenzie (1958*a*). They are mean values obtained from a large number of observations and are believed accurate to ± 1 per cent. It can be seen that the values obtained for the ratio by the two methods are in good agreement.

In the higher current ranges it was possible to make a direct comparison between the modified Brown recorder (4 sec response) and standard Leeds and Northrup Speedomax recorders of 1 and 2 sec nominal balancing time. The maximum current measured on the three instruments agreed to within $\pm 0{\cdot}2$ per cent. As the above measurements were all made using capillaries with drop times in the range 4 to 5 sec, it was considered of interest to compare the three recorders when measuring the maximum current with a capillary of drop time 2 sec. It was found that they agreed within $\pm 0{\cdot}3$ per cent.

The decay of the instantaneous residual current with time has been discussed by one of the authors (McKenzie 1958*b*) elsewhere. The value of the instantaneous residual current at the end of the drop time determined on the modified Brown recorder was in very good agreement with that obtained on the Brush direct writing oscillograph.

All the above measurements show that the instantaneous current at the end of the drop life can be accurately determined with conventional electronic recording equipment.

In Table 2, results are presented for the measurement of half-wave potential and slope. The half-wave potentials (*v.* saturated calomel electrode) have been corrected for iR drop due to the internal and external series resistance of the polarographic cell. Since the total iR drop did not exceed 2 mV at the half-wave point for the solutions examined, the simple iR correction was used (see McKenzie 1955). The values computed from average current were obtained from measurements on a conventional manual polarograph using a Tinsley galvanometer, damped to a half-period of 12 sec, in series with the cell. The half-wave potentials calculated from the maximum current were obtained from measurements with the Brown recorder using manual and automatic recording. The scanning rate for the latter was 100 mV/min. The slopes are obtained from the conventional log plots and have the theoretical values of 0·059 and

0·030 at 25 °C for a 1- and 2-electron reversible reduction respectively (Kolthoff and Lingane 1952). The capillary used had an m value of 1·72 mg sec^{-1} and a drop time in 0·1M KCl at −0·8 V of 4·7 sec.

It can be seen that the half-wave potentials for reversible processes obtained from automatic recording of maximum current are about 2–3 mV more positive than those obtained from manual recording of maximum current. This is due to the voltage scanning effect mentioned earlier in the present paper. The reproducibility of the automatically recorded half-wave potentials is of the order of ±0·5 mV.

TABLE 2

MEASUREMENT OF HALF-WAVE POTENTIAL AND SLOPE AT 25 °C

Solution	From Average Current Galvanometer Manual		From Peak Current			
			Automatic		Manual	
	$E_{\frac{1}{4}}$	Slope	$E_{\frac{1}{4}}$	Slope	$E_{\frac{1}{4}}$	Slope
2×10^{-4}M Pb(II) 2×10^{-4}M HNO_3 1M KCl 0·01% Gelatin	0·432	0·033	0·432	0·033	0·434	0·032
2×10^{-4}M Cd(II) 2×10^{-4}M HNO_3 1M KCl 0·01% Gelatin	0·639	0·030	0·638	0·030	0·641	0·030
2×10^{-4}M Tl(I) 0·1M KCl 0·01% Gelatin	0·459	0·058	0·459	0·059	0·462	0·058
5×10^{-4}M Fe(III) 1M K oxalate No suppressor	0·235	0·057	0·232	0·057	0·235	0·058

The results of Table 2 show also that the respective half-wave potentials of lead(II), cadmium(II), and thallium(I) obtained from *manual* average current measurements are 2 to 3 mV more positive than those obtained from *manual* maximum current measurements. Hume, DeFord, and Cave (1951) have pointed out that both types of measurement should theoretically give the same values. On the other hand, Taylor and Smith (1956) have recently found that the half-wave potential (from average current) of a reversible process varies with the size of the mercury drop and the drop time in the case of the reduction of a metallic ion to a metal soluble in the mercury electrode. However, much less variation was observed for homogeneous electrode reactions. The present authors considered it of interest to see if the half-wave potential of a homogeneous reaction was the same when determined from manual average currents and manual maximum current measurements. In the one case examined, that of

iron(III) in potassium oxalate, it can be seen that both manual methods give the same half-wave potential. However, the voltage scanning effect is still present in the automatically recorded value.

It is to be emphasized that for reversible processes these differences in half-wave potential for the different types of current measurements are small and are mainly of theoretical interest. However, when half-wave potentials are reported it is obviously desirable to state the method of current measurement as well as the capillary characteristics.

IV. General Discussion

During the past 4 years the authors have obtained polarographic waves from manual measurements of average current and measurements of instantaneous current at the end of the drop life. It has been found that the latter type of measurement has a number of advantages. They make possible the automatic recording of polarograms which give accurate values of limiting diffusion current, half-wave potential and slope. Somewhat better current sensitivity and resolution are also obtained.

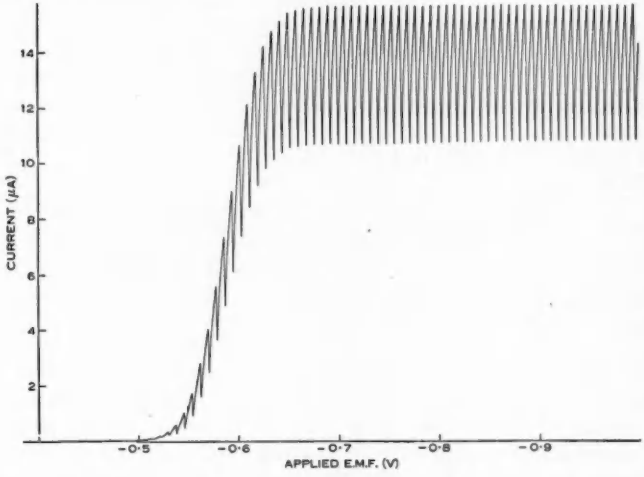

Fig. 2.—Polarogram for 0·002M cadmium(II) in 0·1M potassium nitrate, 0·002M in nitric acid, no suppressor.

One considerable advantage of this method of measurement (both for manual and automatic recording) is that certain abnormalities in polarograms, particularly in current-time curves, can be more easily seen. While the recorders used are not capable of giving accurate current-time curves during the early stages of drop life, they do give a reasonably accurate picture of the current-time relationship during the later stages of drop life. An example of this follows: It has been shown by McKenzie (1958*a*) that in the presence of gelatin

(0·01 g/100 ml) at pH values below its isoelectric point, cadmium(II) in a supporting electrolyte of 0·1M potassium nitrate gives abnormal current-time curves up to an applied e.m.f. of −0·9 V (approx.). This can be clearly seen in curve 1 of Figure 3. It will also be noted that the current-voltage curve is somewhat distorted. Curve 2 of Figure 3 is for 0·001M cadmium(II) in 0·1M potassium nitrate, 0·00001M in nitric acid, and 0·01g/100 ml in gelatin. It can be seen that the current-time curves and the current-voltage curves are normal and like that of Figure 2 which is obtained in the absence of gelatin. Abnormalities of this nature cannot readily be seen from average current-voltage curves obtained using current detectors of slow response speed.

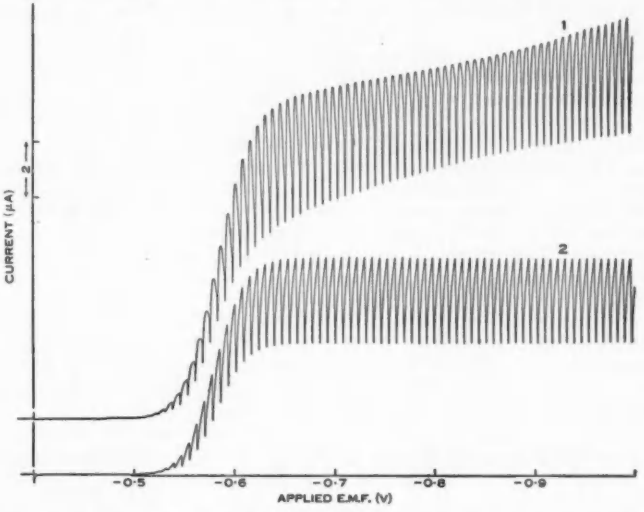

Fig. 3.—Polarograms for cadmium(II) in 0·1M potassium nitrate. Curve 1, 0·002M cadmium, 0·002M nitric acid, 0·01 g/100 ml gelatin. Curve 2, 0·001M cadmium, 0·00001M nitric acid, 0·01 g/100 ml gelatin. (Curves are nested for comparison.)

Against these advantages must be considered the difficulty introduced by the recorder oscillations when it is desired to compensate residual current during measurement of low diffusion currents. A device for controlling the rate of pen drive could be used to eliminate most of the return motion of the pen at drop fall and make it easier to introduce a compensating current which is effective near the end of drop life. The authors' device cannot be used conveniently when the scanning range includes the electrocapillary zero. For this reason the method of Wåhlin and Bresle (1956) has some advantages, and should be studied further.

The present paper shows that instantaneous current at the end of drop life can be conveniently recorded with conventional electronic recorders. In the future, polarographers should be able to obtain data on the variation of maximum

current with capillary characteristics for a large number of capillaries. Providing accurate diffusion coefficient values are available, it should be possible to assess the data in relation to the modified Ilkovic equations.

V. Acknowledgments

Technical assistance from Mr. F. Boland, Mr. M. B. Smith, Mr. S. Rose, and Miss J. Back during the course of this work is acknowledged. Thanks are also due to Messrs. Alfred Snashall Pty. Ltd., and Mr. P. Gibb for the loan of a Speedomax recorder.

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POLAROGRAPHIC CURRENT-TIME CURVES AND THE ILKOVIC EQUATION*

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Summary

The Ilkovic equation for the limiting diffusion current obtained with a dropping mercury electrode predicts that the instantaneous current grows during the life of the mercury drop as the one-sixth power of the time, and that the ratio of the instantaneous current at the end of the drop life (the maximum current) to the average current is 1·17. McKenzie (1948) showed in a preliminary study that these relations are not obeyed.

The present paper is concerned with a more detailed study of current-time curves for cadmium(II), lead(II), and thallium(I) ions and oxygen. Measurements are made both in the presence and absence of maximum suppressor (gelatin) in two supporting electrolytes (potassium chloride and potassium nitrate). It is found that the rate of growth of the instantaneous current is not in accordance with the Ilkovic equation. Also, it does not accurately follow the modified equations, such as the Lingane-Loveridge equation, particularly during the early stages of drop life. The ratio of maximum to average current varies for the different electroactive substances, but in all cases examined $1{\cdot}23 < i_{max.}/i_{av.} < 1{\cdot}30$.

An interesting observation is also made on the current-time curves for cadmium(II) in potassium nitrate in the presence of gelatin. At pH values appreciably below the isoelectric point (~pH 5) the current-time curves and the current-voltage curves are distorted.

The implications of these results in the measurement of polarographic waves, both in theoretical and analytical applications, are discussed.

I. Introduction

In 1922, Heyrovsky introduced the polarographic method of chemical analysis based on the unique characteristics of the current-voltage curves obtained when electroreducible or electro-oxidizable substances are electrolysed in a cell with the dropping mercury electrode and a "non-polarizable" electrode. By 1934 the quantitative interpretation of polarographic processes had been sufficiently developed for Ilkovic (1934) to introduce his well-known equation expressing the relationship between the concentration of electroactive substance and the limiting diffusion current. The equation was subsequently rederived by MacGillavry and Rideal (1937). According to this equation the current (i in μA) at any instant τ (sec) during the life of a mercury drop is given by

$$i = 706nD^{\frac{1}{2}}\ Cm^{\frac{2}{3}}\tau^{\frac{1}{6}},$$

* Based on a communication to the XVth Congress of the International Union of Pure and Applied Chemistry, Lisbon, Portugal, September 1956.

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where n is the number of faradays per mole of reaction, D is the diffusion coefficient of the electroactive substance in $cm^2\ sec^{-1}$, C is its concentration in $mM\ l^{-1}$, m is the rate of flow of mercury in $mg\ sec^{-1}$.

This relation predicts that the current should increase as the one-sixth power of the time during the life of a mercury drop. Thus a plot of $\log i$ *v.* $\log \tau$ should be a straight line of slope 1/6.

The average current during the life of a drop of drop-time t sec is given by

$$i_{av.}=605nD^{\frac{1}{2}}\ Cm^{\frac{2}{3}}t^{\frac{1}{6}}.$$

The maximum current* at the instant before the drop falls is

$$i_{max.}=706nD^{\frac{1}{2}}\ Cm^{\frac{2}{3}}t^{\frac{1}{6}}.$$

It is to be noted that both the maximum current and the average current are directly proportional to the concentration of the substance being electrolysed, and that

$$i_{max.}/i_{av.}=1{\cdot}17.$$

Lingane (1943) introduced the symbol I, which is given by

$$I=i_{av.}/Cm^{\frac{2}{3}}t^{\frac{1}{6}}.$$

Since the value of I should be independent of the electrode capillary characteristics, m and t, Lingane has designated this term the diffusion current constant.

The Ilkovic equation remained unchallenged for over a decade. During 1947 Hamon (personal communication) drew the present author's attention to the fact that the motion of the galvanometer during the measurement of polarographic diffusion currents did not seem to be in accord with the one-sixth power law. Later Hamon and the author attempted to compute the shape of polarographic waves in the presence of large external series resistance by using a graphical construction which assumed the validity of the one-sixth power law. As has been discussed elsewhere (McKenzie 1955) this construction indicated that the one-sixth power law is not valid.

This led the present author to investigate the relation between instantaneous current and time during the life of the mercury drop. In 1948 he (McKenzie 1948) showed that the current does not grow as the one-sixth power of the time as required by the Ilkovic equation.†

At about the same time Steghart (1948) claimed independently that the current does not grow as the one-sixth power of the time during the life of the drop, but varies between one-third and two-thirds power. Also Taylor, Smith, and Cooter (1949) studied the current-time relation using a photographic recording

* The term maximum current, i.e. the instantaneous current at the end of the drop life, is not to be confused with the current observed in the phenomenon of polarographic maxima (Kolthoff and Lingane 1952).

† Owing to an unfortunate typographical error in *J. Amer. Chem. Soc.*, the capillary used has been quoted in the polarographic literature as having a drop time of 0·4 sec instead of 4 sec despite the editor's subsequent corrections (see *J. Amer. Chem. Soc.* **70**: 4279 (1948)).

cathode ray oscillograph. The capillary used had a drop time of 3·5 sec and the solution studied was 0·003M cadmium(II) in 0·1M potassium chloride containing 0·01 per cent. gelatin. They tried to fit their data to an equation of the type $i=k\tau^n$ but found that no single value applied over the entire drop life. From 0·1, 0·5, 1, and 2 sec to the end of the drop life the observed values of n were 0·31, 0·25, 0·23, 0·19 with an average deviation of 5, 1, 0·7, and 0·3 per cent. respectively. Also they found the ratio of $i_{max.}$ to $i_{av.}$ (the graphically integrated average current) to be 1·25, which is significantly greater than the value 1·17 predicted by the Ilkovic equation.

The results of the above investigations led a number of workers to reconsider the theoretical principles underlying the original Ilkovic equation. Lingane and Loveridge (1950) pointed out that although the derivation of the Ilkovic equation begins with the postulate of symmetrical spherical diffusion, the simplification introduced in the intermediate mathematical operations are equivalent to neglecting the curvature of the surface of the electrode. Using a somewhat arbitrary procedure, they showed that

$$i_{av.}=607nD^{\frac{1}{2}}\ Cm^{\frac{2}{3}}t^{\frac{1}{6}}(1+39D^{\frac{1}{2}}m^{-\frac{1}{3}}t^{\frac{1}{6}}).$$

An equation identical with the Lingane-Loveridge equation, but with the numerical constant 17 instead of 39 for the last term, was independently derived by Strehlow and von Stackelberg (1950).

Kambara and Tachi (1951, 1952) have also made a theoretical study of the Ilkovic equation. By treating the problem as a three-dimensional diffusion they derived an equation similar to that obtained by Lingane and Loveridge (1950), and showed that $1\cdot17<i_{max.}/i_{av.}<1\cdot33$. They consider that their equation agrees very well with experimental results given by the present author in his earlier paper (McKenzie 1948).

Recently Koutecký (1952) has derived the following diffusion current equation :

$$i_{av.}=607nD^{\frac{1}{2}}\ Cm^{\frac{2}{3}}t^{\frac{1}{6}}(1+34D^{\frac{1}{2}}\ m^{-\frac{1}{3}}t^{\frac{1}{6}}+100Dm^{-\frac{2}{3}}t^{\frac{1}{3}}).$$

According to von Stackelberg (1953), the term $100Dm^{-\frac{2}{3}}t^{\frac{1}{3}}$ is negligible, and the numerical constant 34 should be replaced by 17 and 607 by 619. Matsuda (1953) has also derived a modified equation which takes into account the screening effect of the capillary.

It will be noted that all the equations for instantaneous current are of the form

$$i=AnD^{\frac{1}{2}}\ Cm^{\frac{2}{3}}\tau^{\frac{1}{6}}(1+BD^{\frac{1}{2}}m^{-\frac{1}{3}}\tau^{\frac{1}{6}}),$$

or

$$i=AnD^{\frac{1}{2}}\ Cm^{\frac{2}{3}}\tau^{\frac{1}{6}}(1+BD^{\frac{1}{2}}m^{-\frac{1}{3}}\tau^{\frac{1}{6}}+EDm^{-\frac{2}{3}}\tau^{\frac{1}{3}}),$$

but that there is some disagreement among workers as to the numerical values of A, B, and E.

No account is taken in the derivation of the Ilkovic or modified equations of the effect of the presence or absence of surface active substances (maximum suppressors) on the observed diffusion current. In this connection the experimental studies of Meites and Meites (1950, 1951) and Meites (1951*a*, 1951*b*)

on factors affecting the diffusion current are of interest. They studied the effect of the capillary characteristics, m and t, on the constancy of $i_{av.}/Cm^{\frac{2}{3}}t^{\frac{1}{6}}$ (the diffusion current " constant ", I) for a number of ions both in the presence and absence of gelatin (0·009 per cent.) as maximum suppressor. Although their work is subject to criticism on the grounds of low ratio of concentration of supporting electrolyte to that of reducible ion and low ratio of galvanometer period to drop time for the capillaries with longer drop time, their results are pertinent. While the exact shape of the I *v.* drop time curves was dependent on the nature of the supporting electrolyte and the ion being reduced, Meites obtained two characteristic types of curves. One, in the presence of gelatin (0·01 per cent.) has a minimum of about 1·5 sec followed by a rising portion (which was treated by a modified form of the Strehlow-von Stackelberg equation) with a maximum at about 6 sec. With the second type of curve, in the absence of gelatin, I is usually invariant between 2 and 7 sec. From the nature of the second type of curve Meites concluded that the original Ilkovic equation fitted it better than the modified equation. It is possible in view of the work of Meites and Meites that the relation between the instantaneous current and the time during the life of the drop approaches also that of Ilkovic in the absence of maximum suppressor. Accordingly, the present author has borne this in mind in extending his earlier work.

Measurements on current-time curves for cadmium(II), thallium(I), lead(II), and oxygen are described below. Some measurements were made in the absence of maximum suppressors, others were made in the presence of gelatin, as maximum suppressor. The two most commonly used supporting electrolytes, potassium chloride and potassium nitrate, were employed. Cadmium, thallium, and lead were chosen since (i) they are commonly determined in polarography, (ii) their reductions are generally considered " reversible ", the rates of their electrode reactions probably being the most favourable of the common inorganic ions (see the k values of Randles and Sommerton 1952*a*, 1952*b*). Oxygen was chosen as it is a simple neutral molecule which is very commonly determined in polarography and it is probably reversibly reduced (see Hacobian 1953).

II. Experimental

The supporting electrolytes were prepared from A.R. reagents which had been twice recrystallized from glass-distilled water solutions. All other reagents were A.R. quality. The solutions used for most of the current-time curve measurements were :

0·01M cadmium(II) in 1M potassium chloride, 0·01M in nitric acid
0·002M cadmium(II) in 1M potassium chloride, 0·002M in nitric acid
0·001M cadmium(II) in 0·1M potassium nitrate, 0·001M in nitric acid
0·002M cadmium(II) in 0·1M potassium nitrate, 0·002M in nitric acid
0·002M cadmium(II) in 0·1M potassium nitrate, 0·00002M in nitric acid
0·001M thallium(I) in 0·1M potassium chloride, 0·0001M in nitric acid
0·002M thallium(I) in 0·1M potassium chloride, 0·0002M in nitric acid
0·002M lead(II) in 1M potassium chloride, 0·002M in nitric acid
Oxygen in 0·1M potassium chloride (air saturated).

The measurements were made at 25 °C. During the course of the work several capillaries were used. Some of these were hand fabricated (HFC) by drawing out capillary tubing in the usual way, others were of the marine barometer tubing (MBT) type. The precaution was taken to see that the capillary was properly cut at the orifice and that the cross section of the orifice was horizontal during the measurements. (Errors arising from failure to observe this precaution have been discussed by Mueller 1944.) It was generally easier to do this with the MBT, hence this type of capillary was preferred. Two capillaries MBT 3 and MBT 6 were mostly used in the experiments reported here. In 0·1M potassium chloride under an applied potential of −0·8 V (*v.* the saturated calomel electrode) their characteristics were:

MBT 3 $m = 1 \cdot 63$ mg sec^{-1}, $t = 4 \cdot 92$ sec measured at $h = 50$ cm
MBT 6 $m = 1 \cdot 84$ mg sec^{-1}, $t = 4 \cdot 29$ sec measured at $h = 40$ cm.

A saturated calomel electrode was used as anode except for one set of measurements with potassium chloride (no gelatin) where a mercury pool anode was used. Oxygen was removed by passage of electrolytic hydrogen purified by passing through the vanadium solution of Meites and Meites (1948).

The instantaneous current was measured by recording the potential drop across a standard resistance. The measuring resistance box was adjusted appropriately so that the voltage drop across it at the end of drop growth was about 50 mV. After amplification with a Brush BL913 amplifier the output was fed into a Brush direct writing oscillograph, type BL202 (Brush Electronics Co., Cleveland, U.S.A.). The BL913 amplifier consists of four stages of amplification and a regulated power supply (see Brush Electronics 1957). The BL202 direct writing oscillograph is designed to make instantaneous permanent chart records of a variety of electrical phenomena (cf. Brush Electronics 1957). When matched with the Brush amplifier it has a flat frequency response between D.C. and 100 c/s. It has nominal chart speeds of 5, 25, 125 mm sec^{-1}. The current-time curves were obtained in each case at an applied e.m.f. which was well in the limiting diffusion region, to allow for the potential drop in the measuring resistance. The corrected applied e.m.f. was −0·75 or −0·8 V in all cases except for oxygen which was −0·45 V. In order that the recorded current shall represent the true current at any time, it is necessary that the reference line for zero current remain constant during the measurements and that the deflections observed be correctly related to the current. Appropriate checks were made for these factors at frequent intervals throughout the measurements. Where there was any evidence of drift etc. the results were discarded. Only if extreme care was taken was it possible to obtain optimum accuracy from the recorder. The precision of the individual current-time curves was of the order of 2 per cent.

Values of the instantaneous current were read from the records at appropriate time values—these were approximately 0·1, 0·2, 0·5, 0·7, 1·0, 1·2, 1·4, 1·6, 1·9, 2·2, 2·5, 3·0, 3·5, 4·0 sec. They were appropriately corrected for residual current. Plots of i *v.* τ and $\log i$ *v.* $\log \tau$ were made.

The ratio $i_{max.}/i_{av.}$ was obtained from the value of $i_{max.}$ observed experimentally and the graphically integrated value of $i_{av.}$.

III. Results and Discussion

(*a*) *Current-Time Curves*

It is not possible to present all the curves showing the relationship between the instantaneous current and the time during the life of the mercury drop. However, the results followed a general pattern. The curves for cadmium(II) in potassium chloride, shown in Figure 1, are typical of this pattern. In all cases the current rose much more slowly in the very early stages of drop life ($<\sim 0{\cdot}2$ sec) than required by the Ilkovic equation. With increasing time the rate of rise became greater than that of Ilkovic, but in the later stages of drop life it decreased again. The slope was then closer to that of Ilkovic but the deviation was still appreciable.

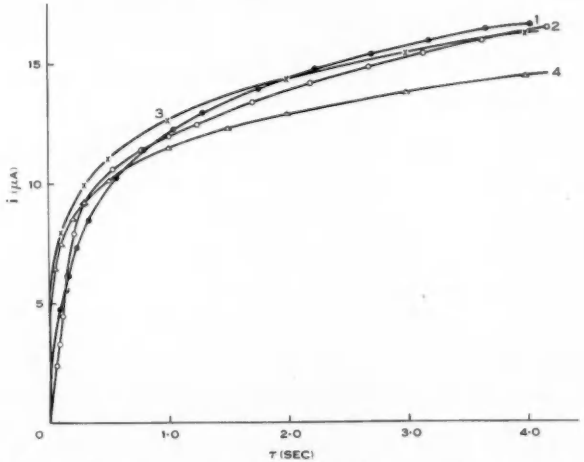

Fig. 1.—Current-time curves for 0·002M cadmium(II) in 1M potassium chloride (0·002M in nitric acid) at —0·8 V. 1, In the presence of 0·01 g/100 ml gelatin; 2, in the absence of suppressor; 3, computed according to the Lingane-Loveridge equation; 4, computed according to the Ilkovic equation.

For cadmium(II), lead(II), and thallium(I) in potassium chloride solution the current rose more rapidly during the early stages of drop life ($<\sim 0{\cdot}1$ sec) in the presence of gelatin than in its absence. With increasing time the rate of rise in the presence of gelatin gradually decreased. In the absence of suppressor the current continued to increase at a fairly steep rate until approximately 0·3 sec, when the slope decreased fairly sharply. These differences can be seen in Figure 1 and in the log plots of Figure 2.

In Figure 1 current-time curves for cadmium(II) in potassium chloride computed from the Ilkovic and Lingane-Loveridge equations are shown for comparison. The value of D was taken as $0{\cdot}73 \times 10^{-5}$ cm^2 sec^{-1}. The Koutecký equation gives curves (not shown) a little lower than the Lingane-Loveridge equation. Deviation of the experimental curves from the Ilkovic equation is

considerable. Somewhat closer agreement is obtained with the modified equation, particularly during later stages of drop life. Allowance was made in the calculated curves for the back pressure effect, which was small. This is obviously not the prime cause of the deviation.

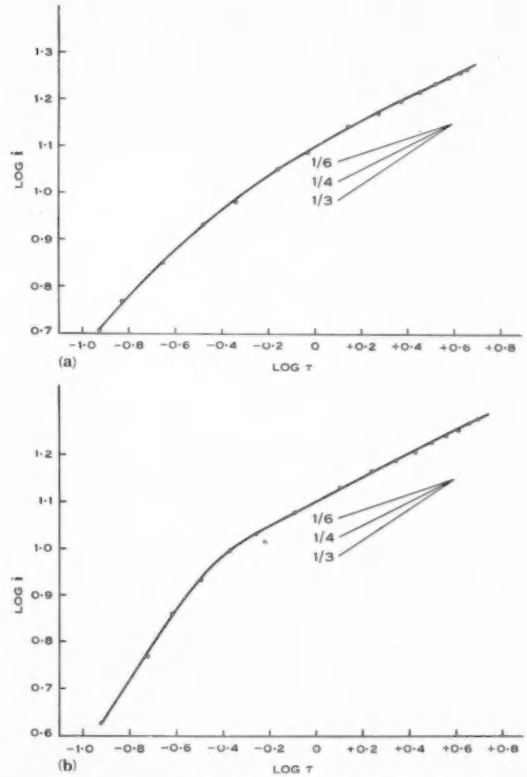

Fig. 2 (*a*).—Log *i*–log τ plot for 0·002M cadmium(II) in 1M potassium chloride (0·002M in nitric acid) in the presence of 0·01 per cent. gelatin at —0·8 V.

Fig. 2 (*b*).—Log *i*–log τ plot for 0·002M cadmium(II) in 1M potassium chloride (0·002M in nitric acid) in the absence of suppressor at —0·8 V.

In Figures 2 and 3, plots are shown for certain solutions of log *i* *v.* log τ from approximately 0·09 sec until the end of the drop time. Lines of slope 1/6, 1/4, and 1/3 are shown for comparison. It can be seen that during the later stage of drop life the log plots are approximately straight lines. In the presence of gelatin from 1 sec approximately to the end of drop time the slope of the line is approximately 1/4. When there is no suppressor this is true from 0·4 sec approximately.

Khalafalla (1953) has reported that, when maximum suppressors are absent, current-time curves for cadmium(II) and thallium(I) in potassium chloride show increasing deviation from the Ilkovic equation with increasing applied e.m.f. No effect of this type was found in the present work.

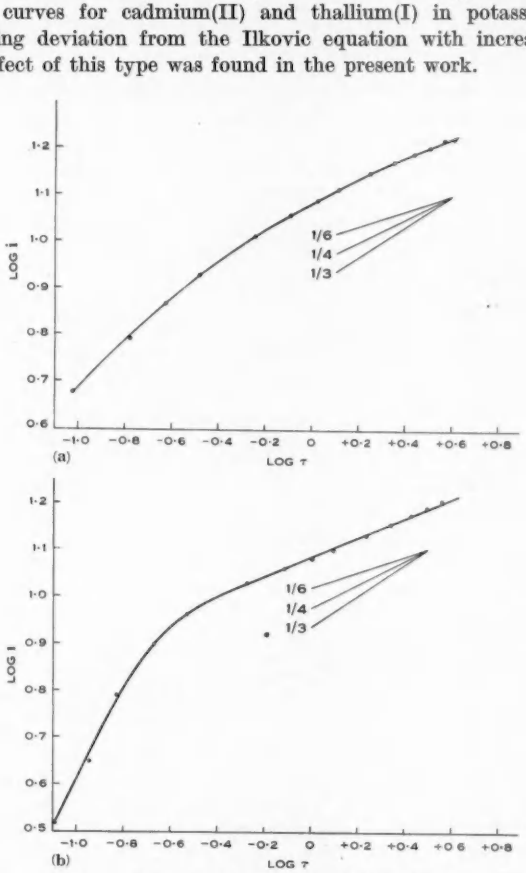

Fig. 3 (*a*).—Log i–log τ plot for 0·002M lead(II) in 1M potassium chloride (0·002M in nitric acid) in the presence of 0·01 per cent. gelatin at —0·8 V.

Fig. 3 (*b*).—Log i–log τ plot for 0·002M lead(II) in 1M potassium chloride (0·002M in nitric acid) in the absence of suppressor at —0·75 V.

The current-time curves for cadmium(II) in potassium nitrate in the absence of maximum suppressor are similar to those in potassium chloride. Measurements were made for 0·001M and 0·002M cadmium(II) in 0·1M potassium nitrate at pH values of *c.* 2·5 and *c.* 5 (pH varied by addition of nitric acid) at applied potentials of —0·75, —0·8, and —1·0 V.

In the presence of 0·01 per cent. gelatin, cadmium(II) in 0·1M potassium nitrate at pH of *c.* 5 gave current-time curves similar to those for cadmium(II)

in potassium chloride (both in 1M and 0·1M KCl over the pH range 2–5). A typical example of such a curve in 0·1M nitrate is shown in Figure 4, curve 3 (applied potential −0·8 V). The current-voltage curves (see McKenzie and Taylor 1958) for these solutions were also normal and reversible. However, the current-voltage curves for cadmium(II) in potassium nitrate in the presence of 0·01 per cent. gelatin at pH values of 2–3 (approximately) were not normal, showing appreciable distortion (see McKenzie and Taylor 1958). Current-time curve measurements at −0·75 V showed that the current-time curves were abnormal at this applied voltage. Similar curves were obtained at −0·8 V,

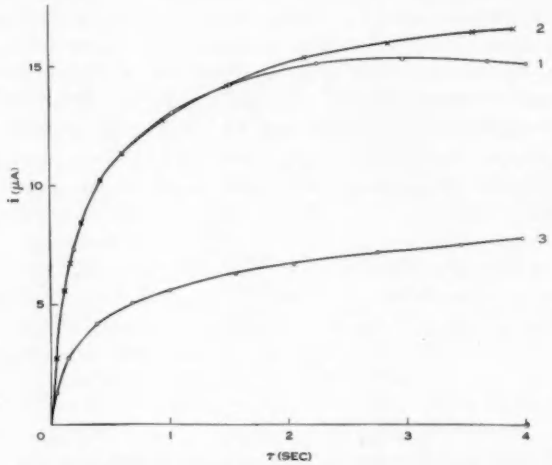

Fig. 4.—Current-time curves for cadmium(II) in 0·1M potassium nitrate in the presence of 0·01 per cent. gelatin. 1, 0·002M cadmium, 0·002M in nitric acid at −0·8 V; 2, same solution at −1·0 V; 3, 0·001M cadmium, 0·00001M in nitric acid at −0·8 V.

a typical curve being shown in Figure 4, curve 1. In a "normal" current-time curve the current increases continually with the time and reaches a maximum at the instant before drop fall. With the abnormal type of current-time curve this is not so. It will be noted that in curve 1 of Figure 4 the current grows until about 3 sec, when it reaches a maximum and then falls off slowly until the end of the drop life. Unlike the current-time curves for reversible reductions, there was an effect of applied voltage on the current-time curves for this irreversible cadmium(II) reduction. When the applied voltage was increased to −1·0 V the current-time curves were normal, Figure 4, curve 2, and $i_{max.}/i_{av.}$ was 1·25. No attempt of course was made to analyse current-time curves, where such abnormalities occurred.

In the presence of 0·002 per cent. gelatin, current-time curves for cadmium(II) in 0·1M potassium nitrate were normal throughout the limiting diffusion region even at low pH.

Current-time curves for 0·002M thallium(I) and 0·002M lead(II) in 0·1M potassium nitrate with 0·01 per cent. gelatin were normal even at pH *c.* 2·5.

These and other experiments indicated that the abnormal behaviour for cadmium(II) in 0·1M potassium nitrate occurs in the presence of gelatin at pH values appreciably below its isoelectric point (~pH 5). Irreversible waves (current-voltage curves) for a number of metal ions have been reported by Tanford (1952) in the presence of acid serum albumin. Tanford has discussed the theoretical significance of the effect and advanced an explanation for it. This explanation is probably valid for the present observations, although not without some interesting complications (McKenzie, unpublished data). It is also of interest to note that Khalafalla (1953) observed abnormal current-time curves for cadmium(II) in solutions containing 0·005 per cent. "Zephiran chloride" as suppressor. The practical importance of these experiments lies in their demonstration of difficulties which may arise in the use of maximum suppressors in analytical polarography.

TABLE 1

THE RATIO OF MAXIMUM CURRENT TO INTEGRATED AVERAGE CURRENT

Ion	Supporting Electrolyte	Suppressor	Capillary	$i_{max.}/i_{av.}$		Number of Observations
				Mean	S*	
Cadmium(II)	1M KCl	Nil	MBT 6	1·244	0·010	5
		0·01 gel	MBT 6	1·246	0·009	12
		0·01 gel	MBT 3	1·25	—	2
Cadmium(II)	0·1M KNO_3	Nil	MBT 3	1·250	0·010	4
		0·01 gel†	MBT 3	1·26	—	2
		0·002 gel	MBT 6	1·24	0·01	3
Lead(II)	0·1M KCl	Nil	MBT 6	1·247	0·012	9
		0·01 gel	MBT 6	1·268	0·012	10
Thallium(I)	0·1M KCl	Nil	MBT 3	1·29	0·02	3
		Nil	MBT 6	1·285	0·021	12
		0·01 gel	MBT 6	1·293	0·012	11
Oxygen	0·1M KCl	0·01 gel	MBT 6	1·29	0·01	3
		0·01 gel	HFC	1·30	—	2

* $S^2=\Sigma d^2/n-1$, where Σd^2 is the sum of squares of deviations from mean and n is the number of observations.

† pH 5 approximately.

(*b*) *Ratio of Maximum to Average Current*

In Table 1 results are shown for the ratio of the maximum current to the graphically integrated average current for the various solutions examined. It is seen that in no case is the ratio in accordance with the simple Ilkovic equation. The ratio is not constant and has different values for different electroactive substances, in accordance with the empirical observations of Furness (1952). In all cases examined by the present author $1{\cdot}23<i_{max.}/i_{av.}<1{\cdot}30$. It should be emphasized that capillaries with drop times in the normal polarographic range 4 to 5 sec were chosen for the present work. Capillaries outside

this range may show even greater deviation from the Ilkovic equation (factors entering are maxima of the " second kind ", effect of back pressure etc.).

It was considered of interest to compute the ratio $i_{max.}/i_{av.}$ for cadmium(II) in potassium chloride predicted by the Lingane-Loveridge equation. This was done assuming $D = 0{\cdot}73 \times 10^{-5}$ cm^2 sec^{-1}. The value obtained was 1·19, which may be compared with the experimental value of 1·245.

(*c*) *General Discussion*

The fact that the current is abnormally small during the early stages of drop life has an important bearing on all the above observations. Various explanations for this effect may be advanced. The most likely is that of Airey and Smales (1950), who first suggested that it is caused by the young drop emerging in that part of the solution whose concentration has been depleted by the reaction at the preceding drop (the " impoverishment " or " depletion " effect). Substantial support for this interpretation has recently been supplied by Hans, Henne, and Meurer (1954). By means of an automatic switching arrangement they recorded i–τ curves for the first drop (of cadmium(II)) in potassium chloride immediately on application of the applied e.m.f. and for the second and subsequent drops. They found the i–τ curve in the presence of gelatin for the first drop is in closer agreement with the modified Ilkovic equation than for the subsequent drops. They interpret this in terms of an impoverishment effect. However, their interpretation is only completely justified if there is no " voltage sweep " effect as the result of the sudden application of the applied e.m.f. They showed that the effect of back pressure was only of secondary importance (except for cylindrical capillaries of high $m^{-\frac{2}{3}}t^{\frac{1}{6}}$ values) in accordance with the present work. Hans, Henne, and Meurer (1954) showed also that the screening of the drop by the capillary and the imperfect spherical shape of the drop were not important factors.

There are at least two factors which are superimposed to give rise to the observed differences in the current-time curves in the presence and absence of gelatin in potassium chloride solution. These are differences in the impoverishment effect and the " rinse " effect (the so-called maxima of the second kind). However, some workers (see, for example, Khalafalla 1953) consider that in the presence of gelatin, the overall reduction is not diffusion controlled. The similarity of the present results on cadmium and thallium, taken along with the work of Hans, Henne, and Meurer, indicate that the deviations are not primarily due to an effect on the electrode reaction velocity. Obviously a further study of these factors is warranted.

The failure of the current-time curves and the ratio $i_{max.}/i_{av.}$ to obey the Ilkovic equation in the absence of gelatin may seem at first sight to be at variance with the observations of Meites and Meites (see Section I) on the nearly constant value of I (in the absence of gelatin) over the drop time range 2–7 sec. However, their results can probably be explained in terms of the " rinse " effect for capillaries with low $m^{-\frac{2}{3}}t^{\frac{1}{6}}$ values, and the back pressure effect for capillaries with high $m^{-\frac{2}{3}}t^{\frac{1}{6}}$ values (see the study of Hans, Henne, and Meurer 1954).

Four implications of the present results on polarographic practice will now be considered, namely : the effect of maximum suppressors ; the ratio of current at the end of the drop life to the average current ; the rate of growth of instantaneous current during the life of the drop ; and the relation of average current to capillary characteristics.

Maximum suppressors have generally been used indiscriminately in polarography (Kolthoff and Lingane 1952). The present work shows that, under certain circumstances, suppressors, such as gelatin, may profoundly affect conditions in the neighbourhood of the mercury drop. Maximum suppressors should be used with caution and then only in amounts adequate to suppress the maximum concerned. When gelatin has been used as suppressor, most authors have used a concentration of the order of 0·01 g/100 ml, whereas 0·002 g/100 ml is frequently sufficient.

The results are conclusive in showing that the ratio of the maximum current to the average current during the life of the mercury drop is greater than that (1·17) predicted by the Ilkovic equation, and no one value applies to all electroactive substances. The rate of growth of current, particularly during the early stages of drop life, is also influenced by a number of factors. In certain studies, values of the instantaneous current or the ratio of the maximum to average current may be required. These can only be obtained if the relations required have been determined for the solution under consideration.

On account of the slow speed of response of the detectors which have been used generally in the measurement of diffusion currents, it has become usual polarographic practice to measure the average current during the life of the mercury drop (see McKenzie and Taylor 1958). The diffusion current " constant " (I) is determined from such measurements. This ratio is not constant for capillaries with different m and t characteristics as first shown by Lingane and Loveridge (1944). While the variation is appreciable, it is not as great as might be expected at first sight from the current-time relations observed in the present work. It is fortunate that during the period when the greatest deviation from the Ilkovic relation occurs, that is, during the early part of the drop life, only a small part of the total quantity of electricity associated with the drop flows. During the later stages of drop life the slope of the current-time curve approaches more closely that predicted by Ilkovic, even though the absolute value of the current is still considerably different from the Ilkovic value (cf. Figs. 1 and 2). Thus I is approximately constant but its value is less precisely predicted by the Ilkovic equation.

The use of diffusion current " constants " computed from average current measurements in analytical polarography is justified only where errors in excess of ± 5 per cent. can be tolerated. Somewhat higher accuracy can be obtained with constants computed by the use of the modified equations (see also the technique of Hans, Henne, and Meurer 1954), but independent calibration of capillaries is preferable.

The present author feels that the thinking of polarographers on these problems has been somewhat obscured by the tradition of measurement of average current. He considers that, for many purposes, it would be preferable

to measure the instantaneous current at the end of the drop life (the maximum current). In this way, effects due to impoverishment of depolarizer, back pressure, and capillary shielding would be largely avoided. At the same time better agreement with the modified equations, such as Lingane-Loveridge and Koutecký, would probably be obtained. The measurement of instantaneous current is discussed further in McKenzie and Taylor's (1958) paper.

Assessment of polarographic data in relation to diffusion current equations would be greatly facilitated if accurate values of diffusion coefficients (D) under polarographic conditions were available. An attempt to obtain such data has recently been made by Wang (1954) and Wang and Polestra (1954) using tracer diffusion. While these data are the best available, the inherent limitations of the tracer technique makes them insufficiently precise to assess accurately the modified equations. In the meantime, the need for accurate diffusion coefficient values and precise data on the variations of average and maximum diffusion current with capillary characteristics on the same solutions cannot be too strongly stressed.

IV. Acknowledgments

The author is indebted to Mr. B. V. Hamon for drawing his attention to this problem and to the Division of Electrotechnology, C.S.I.R.O., for the loan of the recorder used in the measurements. Over the years 1948–55 valuable advice has been given by Messrs. F. Steghart, M. C. Taylor, and M. B. Smith, and Drs. J. J. Lingane, N. H. Furman, J. K. Taylor, and F. E. Huelin. Miss D. Hill and Miss J. Back checked most of the calculations.

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THE PRESSURE EFFECT ON THE RATE OF MENSHUTKIN REACTIONS

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Summary

The rate constants of the reaction between pyridine and ethyl iodide have been measured in acetone at 40 °C and 1, 250, 500, 750, 1000, and 3000 atm. The value ΔV_s of the volume contraction during reaction in acetone solution was also determined. The results obtained lead to the conclusion that the solvation of the transition state in this Menshutkin reaction is considerably less than that of the reaction product.

I. Introduction

The statements in the present paper arise from consideration of Hamann's (1956*a*) paper.

Gonikberg and Povkh (1949) analysed the data of Gibson, Fawcett, and Perrin (1935) concerning the pressure effect on the rate constant of the reaction of pyridine with ethyl iodide in different solvents. This analysis and the density measurements of the reaction product, *N*-ethyl pyridinium iodide, led to the conclusion that " in the reaction of pyridine with ethyl iodide in such different solvents as pyridine and hexane the molar volume of the activated complex is very close to that of the pure liquid reaction product ". In fact, according to the data of Gibson, Fawcett, and Perrin (1935) the values of the rate constants in acetone and hexane at 60 °C, although differing very much from each other, rise equally with pressure increase from 1 to 2890 atm. Thus in both solvents there is an equal volume change ($\Delta V^{\ddagger}$) accompanying the formation of the activated complex (activation volume). Stearn and Eyring (1941) calculated the value of $\Delta V^{\ddagger}$ from the data of Gibson, Fawcett, and Perrin (1935) by the equation (Evans and Polanyi 1935)

$$\Delta V^{\ddagger} = -RT(\mathrm{d}\ln K/\mathrm{d}P) \quad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

(K being the rate constant) and found it to be -20 cm^3 mole^{-1} at 30 °C and 1 atm. On the other hand, the measurement of the volume difference (ΔV_0) between the reaction product and the reactants in the absence of a solvent gave the value $-20{\cdot}5$ cm^3 mole^{-1} (Gonikberg and Povkh 1949).†

The values of ΔV_0 and $\Delta V^{\ddagger}$ being close to each other differed greatly from the volume change accompanying the same reaction in acetone solution (ΔV_s)

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† At 40 °C and 1 atm, $\Delta V_0 \cong -22$ cm^3 mole^{-1}.

measured by Perrin (1938), namely, $\Delta V_s = -54$ cm^3 mole^{-1}. Thus according to the conclusions of Gonikberg and Povkh (1949)

$$-\Delta V_0 \cong -\Delta V^{\ddagger} < -\Delta V_s. \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Recently, Hamann (1956*a*) noticed that Stearn and Eyring (1941) might be considerably in error in their calculations of the $\Delta V^{\ddagger}$ value at 1 atm owing to the absence of experimental data about the pressure effect on the rate constant at pressures below 2890 atm. According to Hamann as well as to Glasstone, Laidler, and Eyring (1941) the transition state in the Menshutkin reactions is almost as highly ionic and extensively solvated as the free ions of the reaction product.* Thus

$$-\Delta V_0 < -\Delta V^{\ddagger} \cong -\Delta V_s. \quad \ldots\ldots\ldots\ldots\ldots (3)$$

However, Hamann did not report new experimental data confirming his views on the reaction discussed. Evidently, for a decision between equations (**2**) and (**3**) it was necessary to measure the rate constant at pressures below 2890 atm in order to estimate with satisfactory exactness the value of $\Delta V^{\ddagger}$ at 1 atm.

II. Results

We measured the rate constants of the reaction of pyridine with ethyl iodide in acetone solution at 40 °C and 1, 250, 500, 750, and 1000 kg cm^{-2} in an apparatus described elsewhere (Gonikberg *et al.* 1956). One experiment was carried out at 3000 kg cm^{-2}.

The pyridine was dried over potassium hydroxide and then rectified in a column of 40 theoretical plates, the fraction with b.p. 115·3 °C/760 mm being collected and used (n_D^{20} 1·5101).

The ethyl iodide was shaken with sulphuric acid (3 vol conc. H_2SO_4 and 1 vol H_2O), separated, and then distilled; b.p. 72·1–72·3 °C/760; n_D^{20} 1·5138. The acetone after boiling with potassium permanganate was fractionated, dried over potassium carbonate, and then distilled; b.p. 56·1 °C/760 mm; n_D^{20} 1·3591; d_4^{20} 0·7912.

The determination of the initial pyridine and ethyl iodide concentrations in acetone solution, the analysis of the samples, and the rate constant calculations were carried out in the same way as in Gibson, Fawcett, and Perrin's (1935) investigation.

The initial concentrations of pyridine as well as of ethyl iodide were about 0·25M (at 20 °C). The calculations of the rate constant included corrections for the change of concentrations due to the compression (using the acetone compressibility data given by Bridgman (1913)) and to the increased temperature (40 °C).

The bimolecular reaction rate constant showed no tendency to change during each experiment; the deviations of the single points from the mean

* An analogous assumption was made by Hamann (1956*b*) in discussing the high pressure kinetic measurements of Weale (1956) of the reaction of *NN*-dimethyl-*o*-toluidine with methyl iodide in acetone solution.

value as a rule did not exceed 4–5 per cent. In each experiment, five samples (each 10 ml) were taken ; the maximal conversion changed from 0·2 (at 1 kg cm^{-2}) to 0·4 (at 1000 kg cm^{-2}).

The results of our determinations are presented in Table 1. At each pressure three parallel experiments were carried out.

TABLE 1

RATE CONSTANTS OF THE REACTION OF PYRIDINE WITH ETHYL IODIDE IN ACETONE AT 40 °C (MIN^{-1} L MOLE^{-1})

Pressure (kg cm^{-2})	Results of Parallel Experiments	Mean Value
1	0·00209, 0·00212, 0·00204	0·00208
250	0·00277, 0·00271, 0·00283	0·00277
500	0·00348, 0·00354, 0·00347	0·00350
750	0·00456, 0·00443, 0·00434	0·00444
1000	0·00539, 0·00524, 0·00544	0·00536

The curve of Figure 1 shows the pressure dependence of log (K_p/K_1) (K_1—the rate constant at 1 atm). The white circle corresponds to the data of Gibson, Fawcett, and Perrin (1935) at 2975 kg cm^{-2} which are in agreement with the result of our experiment at 3000 kg cm^{-2} ($K = 0·0148$). The estimation of $\Delta V^{\ddagger}$ at 1 atm on the basis of the slope of the curve leads to the value $\Delta V^{\ddagger} = -30 \pm 1$ cm^3 mole^{-1}.

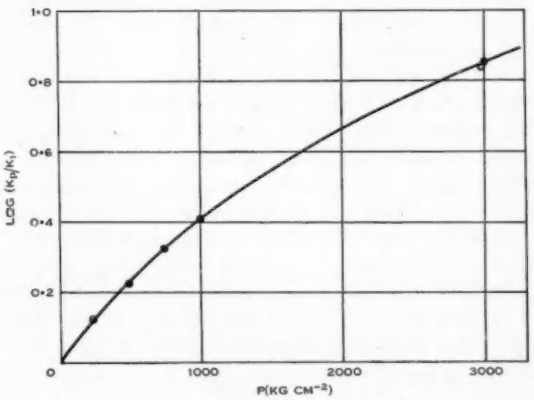

Fig. 1

Further, we measured the value of ΔV_s (the contraction accompanying the reaction in acetone solution). For this purpose we determined the density change of the mixture during reaction. Such a method is believed to be the most correct because it provides the same influence of the concentrations of the reactants and the reaction product on the degree of dissociation and solvation

of the latter as in the actual reaction conditions. The measurements were carried out with 0·25M solutions in a 60 ml pyknometer at 20 °C. The results follow :

Conversion :	0·132	0·268	0·345	0·486
$-\Delta V_s$ (cm^3 $mole^{-1}$).	57·7	56·6	56·3	54·0

We measured also the densities of a 0·12M equimolecular solution of $C_5H_5N+C_2H_5I$ in acetone and of a solution of *N*-ethyl pyridinium iodide having the same molar concentration (corresponding to a conversion of about ·5). These measurements led to a somewhat lower value of ΔV_s ($-\Delta V_s$=48–49 cm^3 $mole^{-1}$) which we believe to be less reliable (for the reason mentioned).

III. Conclusions

It follows from our data that the volume change accompanying the reaction in acetone (ΔV_s) is almost twice as great as the activation volume ($\Delta V^{\ddagger}$). Thus relation (**2**) fits our experimental data better than relation (**3**), following from Hamann's (1956*a*) paper.

To confirm his point of view Hamann refers to the statement of Glasstone, Laidler, and Eyring (1941) that the activation entropy ($\Delta S^{\ddagger}$) in the Menshutkin reactions is nearly the same as the total entropy decrease for the complete reaction (ΔS). This statement was based on the data of Essex and Gelormini (1926), who had calculated the equilibrium constant of the reaction of dimethylaniline with methyl iodide in nitrobenzene. However, these authors had noted that " the determined values of the equilibrium constant may be considerably in error ". An analysis of the data on kinetics and equilibrium of Menshutkin reactions was given in the paper by Syrkin and Gubareva (1938) ; the authors concluded that the difference $\Delta S-\Delta S^{\ddagger}$ is -10 ± 5 e.u. It should be noted that the hydration entropy of the ion I^- is only -4 e.u. (Mischenko 1952). Thus the difference $\Delta S-\Delta S^{\ddagger}$ may be caused to a great extent by the solvation of the ions formed in the dissociation of the reaction product.

The difference between ΔV_0 (-22 cm^3 $mole^{-1}$) and $\Delta V^{\ddagger}$ (-30 cm^3 $mole^{-1}$) as well as the recent data of Weale (1956) showing the somewhat different pressure effect on the reaction of *NN*-dimethyl-*o*-toluidine with methyl iodide in methanol and acetone lead to the conclusion of the solvent participation in the activated complex in Menshutkin reactions. However, the volume effect caused by this participation is several times less than the volume effect of the solvation of ions formed by the reaction product. A possible explanation of this fact may be obtained on the basis of Swain and Eddy's (1948) assumption of the termolecular mechanism of the Menshutkin reactions, but this problem requires further investigation.

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THE S_N MECHANISM IN AROMATIC COMPOUNDS

XXIII. SUBSTITUENT GROUPS ATTACHED BY SATURATED SULPHUR

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Summary

The activating power of *p*-SMe and *p*-SMe_2^+ in aromatic nucleophilic substitution has been compared with available data for $-NH_2$, $-NMe_3^+$, and OMe. The $-SMe_2^+$ group is very powerfully activating and there is strong evidence for a $-T$ effect of $-SMe_2^+$ but not of —SMe, involving expansion of the valency shell beyond an octet. The —SMe group, like —Cl, —Br, and —I, is however also activating, whereas $-NH_2$, —OMe, and —F are more or less deactivating.

I. Introduction

In a previous paper dealing with the substituent effects of *p*-SO_2X groups in aromatic nucleophilic substitution (Heppolette and Miller 1956) it was shown that these were more activating than would be expected if they exhibited inductive (I) effects alone. Evidence that this was due to a conjugative electron-withdrawal ($-T$) supported the view that the valency shell of sulphur is larger than an octet in many compounds. A similar difference in activating power consequent on an additional $-T$ effect was demonstrated by comparison of the diazonium and trimethylammonium groups (Bolto, Liveris, and Miller 1956).

Compared with corresponding elements in the first horizontal period of the Periodic Table, sulphur and other larger elements are thought to have reduced inductive and conjugative effects (Ingold 1953). In aromatic S_N reactions expansion of the valency shell in these larger elements beyond an octet would permit a $-T$ effect even in groups possessing no multiple bonds. These factors should lead to considerable differences between the substituent effects of —SMe and $-SMe_2^+$, and the corresponding nitrogen and oxygen groups, and this is confirmed by the results discussed in the present paper.

II. Results and Discussion

We now present results for the displacement of chlorine in 4-methylthio-, the sulphate of 4-dimethylsulphonium, and the iodide of 4-trimethylammonium-1-chloro-2-nitrobenzenes by absolute methanolic sodium methoxide (Table 1); and compare the substituent effects of these and other groups in Table 2, using the Hammett substituent constants σ or σ^* (Miller 1956).

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TABLE 1

REACTION OF 4-SUBSTITUTED 1-CHLORO-2-NITROBENZENES WITH OMe^-/MeOH

Substituent	k_2 (l mole^{-1} sec^{-1}) at (°C) and [Ionic Strength, μ]	S.R.F.[a] at 50 °C	Arrhenius Parameters		Entropy of Activation, ΔS (e.u.)
			ΔE (kcal)	$\log_{10} B$	
H[b]	$2{\cdot}52\times10^{-6}$ (50·0)[c]	1	23·65	10·4	—13·1
SMe	$5{\cdot}47\times10^{-5}$ (50·0)[c] $7{\cdot}78\times10^{-4}$ (74·3) 1·98 ; $2{\cdot}00\times10^{-3}$ (84·5) $8{\cdot}40\times10^{-3}$ (100·3) $8{\cdot}64\times10^{-3}$ (100·4)	21·7	24·0	12·0	—5·91
SMe_2^+	2·57 ; $2{\cdot}57\times10^{-3}$ (0·0) [0·0440] $5{\cdot}12\times10^{-3}$ [0·0) [0][d] $7{\cdot}45\times10^{-3}$ (9·9) [0·0459] $9{\cdot}60\times10^{-3}$ (9·9) [0·0282] $1{\cdot}01\times10^{-2}$ (9·9) [0·0168] $1{\cdot}07\times10^{-2}$ (9·9) [0·0110] $1{\cdot}615\times10^{-2}$ (9·9) [0][d] 5·00 ; $5{\cdot}08\times10^{-2}$ (25·0) [0·0129] $7{\cdot}90\times10^{-2}$ (25·0) [0][d] $7{\cdot}96\times10^{-1}$ (50) [0][c][d]	$3{\cdot}16\times10^{5}$[e, f]	17·7[f]	11·9[f]	—6·36[f]
NMe_3^+[g]	9·20 ; $9{\cdot}49\times10^{-4}$ (25·0) [0·0130] $3{\cdot}18\times10^{-3}$ (25·0) [0][d] 2·75 ; $2{\cdot}84\times10^{-3}$ (35·2) [0·0130] $1{\cdot}00\times10^{-2}$ (35·2) [0][d] 7·63 ; $7{\cdot}65\times10^{-3}$ (45·25) [0·0130] $8{\cdot}32\times10^{-3}$ (45·25) [0·0117] $1{\cdot}045\times10^{-2}$ (45·25) [0·00820] $1{\cdot}495\times10^{-2}$ (45·25) [0·00383] $3{\cdot}20\times10^{-2}$ (45·25) [0][d] $5{\cdot}36\times10^{-2}$ (50) [0][c][d]	$2{\cdot}13\times10^{4}$[f]	22·2[f]	13·75[f]	+2·21[f]

[a] Substituent rate factor (Miller 1952). [b] Miller (1952). [c] Calc. from experimental k_2 using ΔE (at $\mu=0$ for cations). [d] Experimental correction to $\mu=0$. [e] For comparison, the S.R.F. of the p-NO_2 group at 50 °C = $1{\cdot}14\times10^{5}$. [f] At $\mu=0$. [g] Bunnett *et al.* (1953) presented values of k_2 at $\mu=0{\cdot}015$ somewhat slower than the present work, as would be expected. Their lack of ionic strength correction however puts their values of ΔE and ΔS ($\log_{10} B$ is not quoted) considerably in error.

TABLE 2

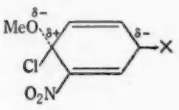
ACTIVATING POWER OF N, O, AND S SUBSTITUENTS

Substituent :	NH_2	OMe	SMe	NMe_3^+	SMe_2^+
Hammett substituent constant (calc. at 50 °C)	—0·883*	—0·512*	0·343	1·110†	1·410†

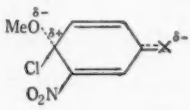
* Slightly different from those computed by Miller (1956) at 0 °C.

† These include the additional activation consequent on reaction being between an anion and a cation (cf. Roberts, Clement, and Drysdale 1951).

For typical reagents such as OMe^-, the authors regard the transition state for attack by anionic reagents as approximating to structures I or II, according to whether the substituent shows a $-I$ or $-I-T$ effect. A *cyclo*hexadienide ring is shown, though probably not fully attained:



(I)



(II)

In this and similar *para*-substituted series we have found in most cases that substituent effects cause changes in ΔE, with ΔS and $\log_{10} B$ little affected, except for anion-anion and anion-cation reactions where theoretically expected changes in the latter are found, while changes in ΔE are still of appropriate sign. This is in contrast with the reaction series discussed by Leffler (1955) where numerically parallel changes in ΔE and ΔS occur.

The changes in ΔE and ΔS for —S, —Cl, —Br, and —I (see below), though somewhat at variance with the normal pattern of our reactions, still do not fit that discussed by Leffler (loc. cit.).

A $-T$ group stabilizes the transition state by extending conjugation and placing negative charge on a hetero-atom. This should result in a large reduction in activation energy ΔE, with the entropy of activation ΔS little changed. In several previous papers (e.g. Miller 1954; Heppolette and Miller 1956), it is shown that the common electron-attracting groups, which are both $-I$ and $-T$, exhibit this behaviour. In the series under consideration typical values are $\Delta\Delta E = c.$ —5 to —7 kcal, and $\Delta\Delta S = c.$ 0 to 4 e.u. for uncharged, including formally dipolar, groups. Correspondingly $+T$ groups such as OMe, NH_2, destabilize the transition state with consequent rise in ΔE.

A $-I$ group can only stabilize the negative charge on the attached ring carbon atom by rendering it more electronegative. In addition, if the substituent group is positively charged stabilization should result from the location of opposite charge on neighbouring atoms. Even with cationic substituents, however, $\Delta\Delta E$ is expected to be considerably smaller than for conjugative groups. The value for the p-NMe_3^+ group (Table 1) is in fact only —1·45 kcal compared with —4·9 for the p-COMe group (Miller 1954), —6·2 for the p-NO_2 group (Beckwith, Miller, and Leahy 1952), and —7·1 estimated for the p-N_2^+ group (Bolto, Liveris, and Miller 1956). A qualitative experiment by Le Fèvre and Le Fèvre (1932) led them to suggest the inferiority of groups acting only via a $-I$ effect.

As regards their $-I$ effect alone the "onium" groups should lie in the order of the electronegativities of the hetero-atoms. This is best represented by Pauling's (1945) electronegativity indices, namely, O^+, 3·8; N^+, 3·3; S^+, 2·8. The relative position of nitrogen and sulphur is confirmed by nitration experiments (Ingold, Shaw, and Wilson 1928; Baker and Moffitt 1930): the $-CH_2SMe_2^+$ group giving only 55 per cent. *meta*-orientation as against 88 per cent. for the

$-CH_2NMe_3^+$ group. Le Fèvre (1929), Le Fèvre and Le Fèvre (1932), and Le Fèvre and Mathur (1930) were in similar experiments unable to obtain useful results in comparing N^+ and O^+, using corresponding quinolinium and pyrylium compounds.

The greater activating power of SMe_2^+ than NMe_3^+ must therefore be due to a $-T$ effect exhibited by the former only, and this is confirmed by the $\Delta\Delta E$ values $= -5 \cdot 95$ and $-1 \cdot 45$ kcal respectively.

The acidity measurements of Bordwell and Boutan (1956*a*) have led them also to postulate such a conjugative effect for the $-SMe_2^+$ but not the $-NMe_3^+$ groups.

The $-NMe_3^+$ compound shows a particularly large value of $\Delta\Delta S = 15 \cdot 3$ for an anion-cation reaction ($\Delta \log_{10} B = 3 \cdot 35$). For the $-SMe_2^+$ compound, $\Delta\Delta S$ is $6 \cdot 74$ ($\Delta \log_{10} B = 1 \cdot 5$). The smaller value may reflect the difference in effectiveness of the charge on a first and second row element, but data quoted in the literature while amply confirming the pattern of the influence of reactions between ions on the entropy term (frequency factor) are too scanty to show whether this difference is a general phenomenon.

Differences between the electrically neutral nitrogen and oxygen groups, and the sulphur group are also striking: the order being $-NH_2 < -OMe < -H < -SMe$. However, the origin of the difference is less clear cut.

In larger atoms both I and T effects are reduced (Ingold 1953). Baker and Hopkins (1949) and Baker, Barrett, and Tweed (1952) have shown for reactions involving equilibria, and favoured in the direction of reactants by electron release, that the combined effects lead to the orders: $-H < -SeMe < -SMe < -OMe$; and $-I < -Br < -Cl < -H < -F$. Bordwell and Boutan (1956*b*), using acidity measurements, have shown the order of electron release: $-SMe < -OMe < -NH_2$, and for phenol but not benzoic acid acidities, that the $-SMe$ was also electron attracting relative to $-H$. Bromination experiments, favoured by electron release, give orders: $-SMe < -OMe$; $-SMe < -NH_2$ (Zincke and Frohneberg 1910; van Hone 1928). In aromatic S_N reactions, Heppolette and Miller (1953) have shown the order of electron attraction: $-H \sim -F < -Cl < -Br < -I$ (rates for $-H$ and $-F$, and for $-Cl$, $-Br$, and $-I$ were shown to be close enough to vary with temperature, but this did not affect the position of the large atoms relative to $-H$ and $-F$). The present reactions show the order of electron attraction:

$$-NH_2 < -OMe < -H < -SMe.$$

There is a general reduction in the extent of conjugative electron release in the reactions and equilibria favoured by electron attraction, and both $-SMe$ and $-F$ are close enough to $-H$ in activating power for the position relative to it to be affected.

Provided there is no $-T$ effect, the substituent effects of the larger neutral groups are the resultant of opposing $-I$ and $+M$ effects of moderate size, and thus large changes in the Arrhenius parameters, especially in ΔE, are unlikely.

As $-I-T$ groups, that is, if valency shell expansion occurs with the neutral single bonded atoms, a considerable reduction in ΔE would be expected. Experimentally (Table 1 and Heppolette and Miller 1953) for —S, —Cl, —Br, and —I, ΔE is little affected, while there is an increase in the entropy term. The details of the latter are uncertain, though it seems to be characteristic of neutral electron attracting groups attached by the larger hetero-atoms.

It seems clear in fact that no $-T$ effect can be postulated for these groups. It has been suggested by Bordwell and Boutan (1956*b*) as a possible explanation of the greater acidity of *p*-methylthiophenol than of phenol, but their result seems to us part of a consistent pattern of a reduced $+M$ effect having a conspicuous result in borderline $-I+M$ groups (see above), and all the substituents they investigated were less electron releasing in the phenols than in the benzoic acids. Correspondingly (cf. Miller 1956) in Hammett plots of nuclear reactions, the use of σ^* rather than σ values (obtained from acidity measurements on phenols and benzoic acids respectively) in no way helps fit electron releasing groups to a linear plot.

Since the $+M$ effect of the larger atoms in S_N reactions plays a conflicting though minor role, it is not surprising that the activating power of —SMe, Cl, Br, and —I with electronegativity indices all between 2·5 and 3·0 are (all) similar.

Comparison of the activating power of $-NMe_3^+$ for chlorine and bromine replacement (Table 1 and Bolto, Liveris, and Miller 1956) confirms that the substituent effect is approximately independent of the halogen displaced (cf. Bolto, Miller, and Williams 1955).

III. Experimental

Runs were carried out using equimolar quantities (varying concentrations up to almost 0·05M) of aromatic compound and sodium methoxide in absolute methanol. Rate constants (k_2) were obtained by graphical plots after estimating Cl^- potentiometrically in aliquots "quenched" in excess dilute Cl^--free nitric acid. Checks of OMe^- consumption were also made potentiometrically. Constants were measured at three temperatures over a range of 20–25 °C for each compound. The Arrhenius parameters (ΔE and $\log_{10} B$) were determined by a least-squares analysis of all determined values of $\log_{10} k_2$ and corresponding reciprocal temperature. The entropies of activation (ΔS) were obtained by standard procedures from k_2 and ΔE and computed at 50 °C. Estimated errors based on reproducibility of k_2 to $\pm 1\frac{1}{2}\%$ are: ΔE, $\pm 0{\cdot}4$ kcal; $\log_{10} B$, $\pm 0{\cdot}3$; ΔS, ± 1 e.u. Ionic strength corrections were made by the usual extrapolation procedure (e.g. Bolto and Miller 1956) and this results in somewhat larger errors for the cationic compounds (probably 50% greater).

Side-reactions with the $-NMe_3^+$ compound could be neglected at the temperatures used to determine chlorine replacement, as indicated by equality of OMe^- and Cl^- liberated. As with the replacement of the corresponding bromo-compound (Bolto, Liveris, and Miller 1956) demethylation occurs however at higher temperatures with enhanced OMe^- consumption. In the case of the $-SMe_2^+$ compound the side-reaction (probably complete replacement of $-SMe_2^+$ as well as demethylation), small at 0 °C but increasing with temperature, could not be neglected, and for this compound both OMe^- consumption, corresponding to total reaction, and Cl^- liberated, corresponding to Cl replacement only, were followed. We then determined the rate of Cl replacement by a simple algebraic procedure (Heppolette and Miller 1953).

(a) Preparation of Materials

(i) p-*Chlorobenzene Sulphonyl Chloride.*—Obtained by a modification of Ullman and Korselt's (1907) procedure in 85% yield (crude).

(ii) p-*Chlorothiophenol.*—From the crude sulphonyl chloride by Otto and Brummer's (1867) procedure. Yield of distilled product=67%.

(iii) *4-Chloro-3-nitrophenyl Dimethylsulphonium Picrate and Sulphate.*—*p*-Chlorothioanisole was heated at 100 °C (water-bath) with a 20% excess of methyl sulphate for 2 hr. The p-*chlorophenyl dimethylsulphonium sulphate* solidified overnight to a wet cake. In separate experiments this was separated, purified, and nitrated. It had m.p. 157–158 °C (decomp.) (in sealed tube) after recrystallization from methanol. The crude salt was nitrated with fuming sulphuric acid (20% SO_3)/conc. nitric acid (3 : 1 v/v). Heat was evolved on mixing after which the temperature fell below 90 °C; it was heated on the water-bath for 2 hr. It was poured onto crushed ice, neutralized with conc. aqueous ammonia, and added to excess saturated aqueous picric acid. The required *4-chloro-3-nitrophenyl dimethylsulphonium picrate* was purified by washing successively with water, methanol, and ether, and obtained in 97% yield having m.p. 153–153·5 °C (decomp.) (sealed tube). The analysis sample was also recrystallized from methanol but with no change in m.p. (Found: C, 38·0; H, 2·6; N, 12·0; S, 7·1; Cl, 8·7%. Calc. for $C_{14}H_{11}N_4O_9SCl$: C, 37·6; H, 2·5; N, 12·5; S, 7·2; Cl, 7·9%). Owing to the inconveniently low solubility (for runs) of the picrate in methanol, the *sulphate* was prepared by anion exchange. It was obtained from the filtrate by standing in a desiccator over conc. sulphuric acid and recrystallized from ethanol by adding ether. It had m.p. 107–108 °C (decomp.) (sealed tube) (Found: C, 35·7; H, 4·3; N, 4·8; O, 24·8; S, 18·3; Cl, 13·3%. Calc. for $C_{16}H_{16}N_2O_8S_2Cl_2$: C, 36·0; H, 3·4; N, 5·2; O, 24·0; S, 18·0; Cl, 13·3%). Before use in runs the compound, which is very hygroscopic, was dried over phosphorus pentoxide in a vacuum.

(iv) *4-Chloro-3-nitrothioanisole.*—The preparation of this utilized the ease of demethylation of the corresponding dimethylsulphonium compound. By a procedure analogous to that used in preparing the sulphate, but using conc. hydrochloric acid, a solution of *4-chloro-3-nitrophenyl dimethylsulphonium chloride* was obtained, but not isolated in solid form. It was diluted threefold and refluxed for 1 hr. The thioanisole was obtained in almost quantitative yield, and after recrystallization from aqueous ethanol had m.p. 73–73·5 °C. Elderfield and Short (1952), who obtained it by another procedure, report m.p. 70–72 °C.

(v) *4-Chloro-3-nitrophenyl Trimethylammonium Iodide.*—This product was prepared by the procedure of Bunnett *et al.* (1953).

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THE S_N MECHANISM IN AROMATIC COMPOUNDS

XXIV. THE POSITIONAL ORDER OF INDUCTIVE EFFECTS IN THE AROMATIC RING

By M. Liveris* and J. Miller*

[*Manuscript received February* 4, 1958]

Summary

The two main views on the transmission of the inductive (I) effect within the ring are tested by comparison of the reactivity of the chlorine in 2-, 3-, and 4-chloro-*N*-methylpyridinium salts with sodium *p*-nitrophenoxide in absolute methanol. Activation by the ring N^+, corresponding to $C^{\delta+}$ for attached $-I$ groups, is shown to be in the positional order: $2 > 4 \gg 3$. The corresponding rate ratios (at 50 °C) are $4{\cdot}89 \times 10^7 : 1{\cdot}62 \times 10^6 : 1$. These results strongly favour the view that both σ- and π-electron systems are involved in the intra-annular transmission. Similar results are obtained for reaction with sodium methoxide in absolute methanol.

I. Introduction

In Miller's (1951) review of aromatic nucleophilic substitution brief reference was made to activation in heterocyclic systems, including pyridine and pyridinium ions. In extending the experimental work to such systems the present authors decided to investigate initially nucleophilic replacement in simple pyridinium compounds, since by doing so a real test of the positional order of the inductive (I) effect within an aromatic ring could be made. The activating power of the ring N^+ relative to other substituents is not discussed in the present paper.

II. Results and Discussion

We have measured the rates of replacement of chlorine in 2-, 3-, and 4-chloro-*N*-methylpyridinium ions by *p*-nitrophenoxide ion in absolute methanol, containing about 2 mole% of *p*-nitrophenol to eliminate concurrent methanolysis (Leahy *et al.* 1956). Although sodium methoxide was used in most of our previous work, it suffers from the disadvantage that it is both very reactive and also demethylates 3-chloro-*N*-methylpyridinium iodide at the higher temperature needed for it (cf. Daly, Kruger, and Miller 1958). We were able however to show definitely the same order of relative reactivity of 3- to 2- and 4-substituents with both reagents (see Section III; also cf. Beckwith, Miller, and Leahy 1952; Leahy *et al.* 1956).

The experimental results, and some derived quantities, are given in Table 1.

There are two main views on the transmission within the aromatic ring of the effect of attached substituents which operate inductively. One (Allan *et al.* 1926; Ingold 1934, 1953*a*; Longuet-Higgins 1957) is that the relay involves both the σ- and π-electron systems. The other (Roberts, Clement, and Drysdale 1951; Roberts and Moreland 1953; Roberts and Carboni 1955) is that only the

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TABLE 1

REACTION OF CHLORO-*N*-METHYLPYRIDINIUM SALTS WITH SODIUM *p*-NITROPHENOXIDE IN METHANOL

Position of Cl	Temp. (°C)	Rate Constant (l mole^{-1} sec^{-1}) (*a*) At μ=[ ] and (*b*) At μ=0	Arrhenius Parameters at μ=0		Entropy of Activation, ΔS^* (e.u.)
			ΔE (kcal)	$\log_{10} B$	
2	0	1·80 ; 1·825×10^{-2} [0·0760] 6·91 ; 6·99×10^{-2}			
	10·1	5·75 ; 5·81 ×10^{-2} [0·0760] 2·32 ; 2·35×10^{-1}			
		7·24 ×10^{-2} [0·0543] —			
		8·95 ×10^{-2} [0·0380] —	18·6	14·3	+4·74
		1·10 ×10^{-1} [0·0190] —			
	17·9	1·33$_6$; 1·36$_5$ ×10^{-1} [0·0760] 5·63 ; 5·76×10^{-1}			
	50	— — 1·39×10†			
3	50	— — 2·84×10^{-2}†			
	120·0	4·63 ; 4·70 ×10^{-4} [0·0418] 1·22 ; 1·24×10^{-3}			
	131·0	1·18$_5$; 1·21 ×10^{-3} [0·0418] 3·50 ; 3·56×10^{-3}	30·2	13·9	+2·82
		1·52 ×10^{-3} [0·0268]			
		1·72 ; 1·80 ×10^{-3} [0·0161]			
	138·8	2·17 ; 2·20 ×10^{-3} [0·0418] 7·11 ; 7·21×10^{-3}			
4	0	— — 3·05×10^{-3}†			
	10·1	2·76 ; 2·82 ×10^{-3} [0·0418] 9·58 ; 9·78×10^{-3}			
	25·0	1·21 ; 1·22 ×10^{-3} [0·0418] 4·53 ; 4·57×10^{-2}			
		1·76 ×10^{-3} [0·0209] —	17·6	11·6	—7·76
		1·90 ×10^{-3} [0·0157] —			
		2·52 ×10^{-3} [0·0143] —			
	35·3	3·12 ; 3·19 ×10^{-3} [0·0418] 1·23 ; 1·26×10^{-1}			
	50	4·60×10^{-1}†			

* At 50 °C and μ=0.

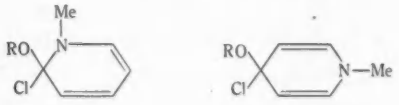
† Calculated using ΔE.

σ-bond relay is effective. In addition however there is general acceptance of a direct (*D*) effect not operating through the bonds. A $-I$ group may be said to initiate the intra-annular transmission via an electron deficient ring carbon atom ($C^{\delta+}$) at the point of attachment. The pyridinium system simply substitutes the more effective N^+. In addition, the explanation of *meta*-direction by such groups as $-NMe_3^+$ in S_E reactions, by those denying π-bond relay, as due to destabilization of the *ortho*- and *para*-transition states because of like charges on neighbouring atoms (Roberts, Clement, and Drysdale 1951) would lead correspondingly in the pyridinium S_N reactions to stabilization of the 3- (or *meta*-) transition state (shown most clearly by an extreme representation as structure I). There *unlike* charges are on neighbouring atoms in the 3- but not 2- and 4-transition states.

(I)

Our results show the overwhelming superiority of 2- and 4- (corresponding to *ortho*- and *para*-) over 3- (or *meta*-) activation. From Table 1 the rate k_2 ratios at 50 °C may be computed as: $o : m : p$ $4{\cdot}89\times10^7 : 1 : 1{\cdot}62\times10^6$. The view that the π-electron system is involved, and indeed plays the major role, is thus fully supported. Correspondingly the activation energies ΔE are in the order: 2-, 4-$\leqslant$3.

For typical reagents such as OR^- we regard the transition states in aromatic S_N reactions as approaching a *cyclo*hexadienide structure (e.g. Daly, Kruger, and Miller 1958). The 3-transition state has been shown as I. The 2- and 4-transition states may be shown similarly in extreme forms as II and III. The latter are more stable since the extra pair of electrons is located on an initially positive



(II) (III)

nitrogen whereas in the former it is on the much less electronegative carbon atom adjacent to a positive nitrogen, though even there some activation will occur (cf. Ingold 1953, p. 248; Brown and Hefferman 1957). With an attached group such as $-NMe_3^+$ there is a corresponding difference between location on a carbon atom adjacent to, and one which is two atoms from, a positive nitrogen.

The situation in 3-chloro-*N*-methylpyridinium iodide and the iodide of 1-chloro-2-nitro-4-trimethylammoniumbenzene is seen to be somewhat analogous (though favouring the former). The relative rates for methanolysis of these two compounds (about 10^{-4} and 6×10^{-2} respectively at 50 °C) are of the right order of magnitude for this, allowing for the additional activation by a nitro group in the latter.

In alternative terminology, the major effect of the more electronegative ring atom, whether the result of attachment of an inductive electron attracting group or the substitution of a hetero-atom in the ring, is relayed to the 2- and 4-positions, and much less to the 3-position. This depends on the π-electron system, but is not concerned with extension of conjugation outside the ring. It does not involve relay along a series of σ bonds. It does not utilize any *D* effect.

Roberts, Clement, and Drysdale (1951) and Roberts and Moreland (1953) base their disregard of π-electron transmission on measurements of relative acidities, particularly of $-NMe_3^+$ compounds; but these are comparatively insensitive and are also equilibrium reactions (cf. substituted fluorobenzenes, Miller 1956) in which permanent conjugative effects only could be expected; while the *D* effect could influence the order of the ammonium compounds (Ingold 1953, pp. 254, 732). The acidities of *m*- and *p*-NMe_3^+ compounds are in fact very close.

The differences between the substituent effects in *para*-substituted benzoic acids and 4-substituted *bicyclo*-[2,2,2]-octane-1-carboxylic acids though small do not in our view indicate therefore the absence of internal conjugative transmission in the former, since these carboxylic acid systems are particularly insensitive to substituent effects, and the substituents were not well chosen to demonstrate the differences.

The Arrhenius parameters confirm the general discussion. Despite the suggested electrostatic stabilization of the 3- but not 2- and 4-transition states, the activation energies of the latter are much lower than the 3-compound.

The entropy terms (frequency factors) are all high as expected for anion-cation reactions, though the value for the 4-compound is considerably lower than the others. A possible reason for this difference is that with *para*- known to be more stable than *ortho*-quinonoid type structures (Ingold 1953, p. 267) the *para*-transition state may not involve as great a movement towards the fully *cyclo*hexadienide structure, and with the remaining charge well separated the loss of solvation would be less in such a case, with smaller increase in entropy.

III. Experimental

Runs were carried out using equimolar quantities (see Table 1) of the pyridinium compound and sodium *p*-nitrophenoxide in absolute methanol, together with a tenfold excess of the free phenol (<2 mole%). Rate constants (k_2) were obtained by graphical plots after estimating Cl^- potentiometrically in aliquots " quenched " in excess dilute chloride-free nitric acid. Constants were measured at three temperatures for each compound spread over about 20 °C. Ionic strength (μ) corrections are considerable and were made in the usual way (e.g. Bolto and Miller 1956) by extrapolation of experimental points put on to a $\log_{10} k_2$—$\mu^{\frac{1}{2}}$ plot. The extrapolated values are naturally less accurate than the directly determined rates. Arrhenius parameters were determined by a least-squares analysis of the values of $\log_{10} k_2$, at $\mu=0$, and reciprocal temperature. Entropies of activation (ΔS) were obtained by standard procedures from k_2 and ΔE and computed at 50 °C. Runs gave good second-order plots without indications of side reactions; e.g. a least-squares plot for reaction of 2-chloro-*N*-methylpyridinium picrate and sodium *p*-nitrophenoxide (0·038M) in methanol at 0·0 °C gave $k_2=1{\cdot}834\pm0{\cdot}013\times10^{-2}$ l mole^{-1} sec^{-1}.

Because of the need to use extrapolated values of k_2 (at $\mu=0$) in determining derived data, the estimated maximum errors are larger than usual: ΔE, $\pm0{\cdot}6$ kcal; $\log_{10} B$, $\pm0{\cdot}5$; ΔS, $\pm1{\cdot}5$ e.u.

(a) Preparation of Materials

(i) *2-Chloro-N-methylpyridinium Salts.*—The *p*-toluenesulphonate was prepared by a modification of Marvel, Scott, and Amstutz (1929) procedure. The product, m.p. 118–119 °C (lit. 119–120 °C), was hygroscopic, and was converted to the *picrate* by a standard method. It had m.p. 106–107 °C (Found: C, 40·8; H, 2·5; Cl, 10·1%. Calc. for $C_{12}H_8N_4O_7Cl$: C, 40·4; H, 2·5; Cl, 9·9%). This salt was used for most runs, however, since the iodides of the 3- and 4-compounds were used for runs it was necessary to confirm that the anion had no influence. This was done by carrying out two of the runs with the iodide of the 2-compound.

An unsuccessful attempt to make the iodide by the usual procedure from 2-chloropyridine was made by Bradlow and van der Werf (1951), who obtained the ring iodo-compound instead. We suspected that this was the result of a subsequent displacement of chlorine by the moderately nucleophilic iodide ion, and that the required compound would result at low temperatures. This was found to be the case: equimolar quantities of 2-chloropyridine and methyl iodide stood below 0 °C for 3 days formed a crystalline mass of the *iodide*, which was purified by precipitating with ether from ethanolic solution and formed almost colourless needles, m.p. 207 °C. This is the same m.p. as the 2-iodo-*N*-methylpyridinium iodide obtained by Bradlow and van der Werf (1951), however our compound analysed correctly; had no ionic chlorine; and was readily converted to the iodine-free picrate giving no depression of m.p. with an authentic sample (Found: C, 27·9; H, 3·0; I, 49·3%. Calc. for C_6H_7ClNI: C, 28·2; H, 2·8; I, 49·7%).

(ii) *3-Chloro-N-methylpyridinium Iodide.*—This was made by the standard procedure from 3-chloropyridine, and after recrystallization with ethanol-ether gave colourless needles, m.p. 141–142 °C (Found: C, 28·3; H, 2·9; Cl, 14·6%. Calc. for C_6H_7ClNI: C, 28·2; H, 2·8; Cl, 13·9%). The *picrate* was also prepared and had m.p. 128 °C (Found: C, 40·4; H, 2·7; Cl, 9·7%. Calc. for $C_{12}H_8O_7ClN_4$: C, 40·4; H, 2·5; Cl, 9·9%).

(iii) *4-Chloro-N-methylpyridinium Iodide.*—This was made by the procedure of Sprague and Brooker (1937) and had m.p. 161–162 °C (lit. 161–163 °C).

(b) Methoxide Experiments

In separate experiments known equimolar quantities of the 2- and 4-pyridinium compounds and sodium methoxide in methanol reacted completely (shown by Cl^- produced) at −15 °C within 2 min, whereas the 3-pyridinium compound reacted quite slowly at 45 and 60 °C, and this reaction included demethylation as well as chlorine replacement. The order $o, p \gg m$ is thus confirmed for this reagent also.

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THE S_N MECHANISM IN AROMATIC COMPOUNDS

XXV. SUBSTITUENT EFFECTS OF MULTIPLE-BOND NITROGEN

By J. MILLER* and A. J. PARKER*

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Summary

The substituent effects in aromatic nucleophilic substitution of groups attached to the benzene ring by a multiple-bond nitrogen atom are considered. Attachment is *para* to a replaceable halogen atom, and generally as a 4-substituent to 1-chloro-2-nitrobenzene. Comparisons with some other groups are shown.

Reasons are given for the greater T effect of a triple than of a double bond. Hammett substituent constants (σ^*) are computed. Those for the nitroso and diazonium groups are the largest so far obtained for electrically neutral and cationic groups respectively.

The activating power of four of the nitrogen groups in electrophilic as well as nucleophilic substitution is discussed briefly.

I. INTRODUCTION

The present paper considers the substituent effects, in typical activated nucleophilic substitution, of the common groups in which multiple-bond nitrogen is attached directly to a benzene ring, *para* to a replaceable halogen atom, and with measurements made or estimated for reaction of 4-substituted 1-chloro-2-nitrobenzenes with absolute methanolic methoxide. Table 1 lists these groups, together with data, used in discussion. The new experimental results are given in Tables 2 and 3.

II. RESULTS AND DISCUSSION

Electron attracting groups activate aromatic nucleophilic substitutions by placing the negative charge of a *cyclo*hexadienide type transition state on an electronegative atom in the substituent and extending the conjugation ($-T$ groups), or less effectively by rendering an acceptor ring carbon atom more electronegative ($-I$ groups) (Miller 1951 ; Bolto and Miller 1956 ; Daly, Kruger, and Miller 1958).

The seven nitrogen groups, which appear in groups (i) and (iii) of Miller's (1951) classification or have been commented on by Heppolette, Miller, and Parker (1954), are each bound to the ring containing replaceable halogen by a (α-) nitrogen atom which is formally either neutral, positively polar, or dipolar. This should lead them to behave as $-I$ groups, though the effect is reduced in the azido- and α-phenylazoxy groups by internal conjugation placing a fractional negative charge on the α-nitrogen atom. It is more important in the former,

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TABLE 1

METHANOLYSIS OF 4-SUBSTITUTED 1-CHLORO-2-NITROBENZENES*

4-Substituted:	Activation Energy, ΔE (kcal)	Frequency Factor ($\log_{10} B$)	Entropy of Activation, ΔS (e.u.)	Rate Constant (k_2) at 0 °C (l mole^{-1} sec^{-1})	Substituent Rate Factor (S.R.F.)†	Hammett Substituent Constant (σ^*)
—H	23·65	10·4	—12·8	$2·97\times10^{-9}$	1	0
—N=$\overset{+}{\text{N}}$=N$^-$	24·2	11·25	—9·02	$7·15\times10^{-9}$	2·41	0·083
—N=$\overset{+}{\text{N}}$Ph[a, b] (O$^-$)	21·1	11·0	—9·63	$1·59\times10^{-6}$	$5·35\times10^{2}$	0·595
—N=NPh[c]	20·3	10·8	—11·2	$3·16\times10^{-6}$	$1·07\times10^{3}$	0·659
—$\overset{+}{\text{N}}$=NPh[d] (O$^-$)	19·5	10·6	—11·9	$9·84\times10^{-6}$	$3·31\times10^{3}$	0·769
—C(Me)=O	18·75	10·4	—12·8	$2·40\times10^{-5}$	$8·08\times10^{3}$	0·874
—CH=O[e]	—	—	—	$6·00\times10^{-5}$	$2·02\times10^{4}$	0·939
—C≡N[e]	—	—	—	$1·13\times10^{-4}$	$3·81\times10^{4}$	0·997
—$\overset{+}{\text{N}}$=O (O$^-$)	17·45	11·25	—8·81	$2·00\times10^{-3}$	$6·73\times10^{5}$	1·270
—N=O	16·2	11·15	—9·32	$1·55\times10^{-2}$	$5·22\times10^{6}$	1·463
—$\overset{+}{\text{N}}$≡N[f]	16·55	13·3	+0·93	1·41	$3·83\times10^{8}$	1·870

* Experimental results are in Tables 2 and 3 or in references in the text.

† Miller (1952).

[a] α-Phenylazoxy (cf. Sidgwick 1942). [b] Calculated in methanol using comparative values obtained with the nitro- and the β-phenylazoxy compound (see text). [c] Bunnett, Moe, and Knutson (1954) obtained very similar rate constants but measured over 10 °C only and their values of ΔE and ΔS differ somewhat from ours. [d] β-Phenylazoxy (cf. Sidgwick 1942). [e] Estimated by using the Hammett equation to relate two similar reaction series (Miller 1956; Miller, Parker, and Bolto 1957). [f] Estimated after relating values for OMe^-/MeOH and OH^-/H_2O with the $—N^+Me_3$ compound (Bolto, Liveris, and Miller 1956; Daly, Kruger, and Miller 1958); using the Hammett equation to relate two similar reaction series (Miller 1956); and using also ΔE and derived values to estimate corresponding values for the diazonium compound.

TABLE 2

METHANOLYSIS OF 4-SUBSTITUTED 1-CHLORO-2-NITROBENZENES (OMe^-/MeOH)*

4-Substituted:	$-N_2$	$-N_2Ph$†	$-N(O)=NPh$	$-NO$
10^5k_2	18·0; 18·5 (80·2 °C)	66·5; 66·9 (45·55 °C)	159; 162 (45·2 °C)	357; 357 (—13·0 °C) (—13·15 °C)
	121; 121 (101·0 °C)	260; 261 (60·2 °C)	664; 665 (60·4 °C)	1460; 1460; 1570 (0·0 °C)
	650; 656 (121·2 °C)	1760; 1810 (81·9 °C)	3420; 3440 (80·2 °C)	4060 (8·85 °C)
				6790; 6840 (14·25 °C)

* For $-N_2^+$ see footnote to Table 1; for $-NO_2$ see Beckwith, Miller, and Leahy (1952); Arrhenius parameters, ΔS, and k_2 at 0 °C see Table 1.

† k_2 and σ^* at 50 °C reported by Miller (1956).

TABLE 3

HYDROLYSIS OF 4-SUBSTITUTED 1-CHLORO-2-NITROBENZENES (OH^-/DIOXAN-WATER 3 : 1)

4-Substituted:	$-N=N(O)Ph$	$-N(O)=NPh$	$-NO_2$
10^5k_2	0·00708[a] (0 °C)	0·0441[a] (0 °C)	8·81[a] (0 °C)
	7·29; 7·31 (60·4 °C)	7·04; 7·05 (45·3 °C)	29·4 (10·2 °C)
	45·0; 45·7 (80·8 °C)	27·0; 27·6 (60·4 °C)	128; 128 (25·0 °C)
	218 (100·6 °C)	166; 170 (80·8 °C)	327; 333 (35·0 °C)
	230 (100·7 °C)	630; 633 (100·6 °C)	723 (45·2 °C)
ΔE and $\Delta\Delta E$[b]	20·85 (+0·25)[c]	19·35 (+0·15)	17·1 (+0·35)
$\text{Log}_{10}B$ and $\Delta\log_{10}B$[b]	9·55 (+1·45)[c]	9·15 (+1·45)	9·8 (+1·45)
ΔS and $\Delta\Delta S$[b]	—16·7 (+7·1)[c]	—18·6 (+6·7)	—16·3 (+7·5)
k_2 ratio	22·5[c]	22·3	22·7

[a] Calculated using ΔE. [b] Required to give values with OMe^-/MeOH. [c] Average value used to compute values with OMe^-/MeOH.

being spread over two nitrogen atoms, and results in approximate cancellation of the $-I$ effect (cf. Bassett, Brown, and Penfold (1956) on the electronegativity of heterocyclic nitrogen).

In all these groups there is also available in these reactions a conjugative electron withdrawal resulting from the $\alpha\beta$-multiple bond. In some cases internal conjugation stabilizes the initial state and competes with or opposes the extension of conjugation in the transition state (Ingold 1953, pp. 77, 266). It is marked in the nitro- (cf. carboxylate), azido-, and the two phenylazoxy groups.

While orders of $-I$ and $-T$ effects can be predicted reasonably on the basis used by Ingold (1953, pp. 61–92), their combination to give the overall effect is to some extent subjective, and is therefore not attempted. It is clear, however, that the diazonium-, nitro-, and nitroso-groups which have powerful $-I$ and $-T$ effects should be considerably more activating than the other four groups as is found. The first place of the diazonium group however seems to be due essentially to the fact that reaction is there between an anion and cation. These results, the results of Miller, Parker, and Bolto (1957) in comparing $-C{\equiv}N$ and $-C{=}O$, and general aromatic and aliphatic chemistry, indicate that the $-T$ effect of a triple bond is greater than that of the corresponding double bond, and that $\equiv N$ is comparable to $=O$ in this respect.

This seems not to have been discussed before. In our view it stems from the virtual independence of movement of the two pairs of π-electrons in a triple bond. The charge displacement resulting from the movement of the conjugated π-electrons, tending to a state of higher potential energy, is compensated in the triple bond by the movement of the second pair of π-electrons in the opposite direction. The total polarization during reaction can thus involve a greater displacement of the conjugated π-electrons than is possible in a double bond.

In commenting on the limitation of $-T$ effect by internal conjugation, Ingold (1953, pp. 77, 266) specifically quoted the order: nitroso$>$nitro. Our results give comparative rates. The difference is much less than that found (by comparing percentage products) by Le Fèvre (1931) for an S_N-1 like reaction. In general, behaviour groups such as aldehyde, methylketo, and nitrile (Miller 1954; Miller, Parker, and Bolto 1957) resemble the nitroso-group, and the sulphone type groups (Heppolette and Miller 1954, 1956) resemble the nitro-group.

The lesser activating power of the azo, azido, and two phenylazoxy groups results from the lesser $-T$ effect of $=N$ than $=O$. All four except the azo-group suffer from internal conjugation, and of these only the β-phenylazoxy group attached by positively dipolar nitrogen is more activating than it.

The Arrhenius parameters and ΔS values are in accord with the discussion. The powerful $-T$ groups have $\Delta\Delta E$ values of *c.* -6 to -7 kcal; the azido group is scarcely changed; while the other three groups have values *c.* $-2{\cdot}5$ to -4 kcal. Only the cationic diazonium group has large changes in $\Delta\log_{10} B$ and $\Delta\Delta S$, in the form of a large increase as expected.

The azido-, phenylazo-, α-phenylazoxy-, and nitroso-groups are attached to the ring by formally neutral nitrogen, thus having a pair of unshared electrons.

They should therefore be classified as $-I$ $+T$ groups in aromatic S_E reactions, and the azido- and α-phenylazoxy groups in particular are likely to be activating as well as *ortho-para* directing. Appropriate results are so far available only for the phenylazo-group which is slightly activating for bromination by Br_2 (Robertson, de la Mare, and Swedlund 1953). These four groups, together with, for example, attached and fused benzene rings and the heterocyclic *N*-oxide group, activate in both S_E and S_N reactions.

The Hammett equation has already been applied by Miller (1956) to the 4-substituted 1-chloro-2-nitrobenzenes among others, and we have therefore calculated new substituent constants (σ^*), viz. for the azido-, α- and β-phenylazoxy-, and nitroso-groups (Table 1). Based on this work, Miller (1956) has reported k_2 and σ^* at 50 °C for the phenylazo-compound. Difficulties which can be caused by easy reduction of the nitroso-group are indicated in the kinetics obtained; and also by some qualitative experiments with *ortho-* and *para*-chloronitrosobenzenes (see p. 307).

III. Experimental

(a) *Kinetic Runs*

These were mostly carried out with equimolar concentrations of compound and sodium methoxide in absolute methanol, from about 0·02 to 0·05M in different runs. There were occasional runs with about 50% excess of methoxide. Further runs were carried out with potassium hydroxide in 75/25 (v/v %) dioxan-water: in these, difficulties were experienced due to alkali-glass reaction, which is more extensive in dioxan-water than in water alone but was less in soda than Pyrex glass. This side reaction was not serious enough to interfere with determination of rate constants in the first third of the reaction: it was also minimized by using the lowest possible temperatures. The hydroxide reactions require 2 moles of reagent per mole of aromatic compound, since the product is acidic (cf. Brady and Miller 1953).

In the usual conditions (OMe^-/MeOH) side reactions occurred with the azido- and nitroso-compounds, but not so much as to prevent satisfactory rate measurements. With the azido-compound nitrogen was evolved in the late parts of runs, and rate plots began to tail off. Reduction began to interfere with the nitroso-compound measurements after about one half-life, and methoxide consumption then began to exceed chloride formation. The side reaction was relatively less important at lower temperatures, indicating the greater activation energy of the reduction process. For both these compounds rate constants were determined only during about the first half-life.

The measurements with hydroxide in dioxan-water were made particularly because the solubility of the α-phenylazoxy compound in methanol was inconveniently low for runs. To compute results for this compound for methanolic methoxide the relationship found for the similarly dipolar nitro- and β-phenylazoxy compounds was used (see Table 3).

Rate constants (k_2) were obtained by graphical plots after estimation of chloride ion potentiometrically in aliquot parts " quenched " in excess of chloride-free dilute nitric acid. Occasional runs however were also measured by " quenching " aliquot parts in known excess of standard dilute hydrochloric acid and back-titrating potentiometrically.

Constants were measured at not less than three temperatures for each compound covering 25 °C or more. The activation energy (ΔE) was determined by a least-squares analysis of all determined values of k_2 and reciprocal temperature, and values of $\log_{10} B$ and ΔS (at 0 °C) determined in the usual way.

With few exceptions duplicate runs agreed within ±2% or less. However, a general error of ±3% has been assumed, giving maximum errors: ΔE, ±0·6 kcal; $\log_{10} B$, ±0·4; ΔS, ±1·5 e.u.

(*b*) *Thermostats*

For temperatures above about 80 °C a vapour-bath type was used; for temperatures below 0 °C a refrigerator type was used; and for intermediate temperatures the usual type with either a permanent heater for above-room temperature or an ice-canister for permanent cooling between 0 °C and room temperature. Apart from the vapour-bath type, toluene mercury regulators were used.

(*c*) *Qualitative Experiments with* o- *and* p-*Chloronitrosobenzenes*

By correlation of the present results with those presented by Miller (1956), and the facile reduction of nitroso-compounds by methoxide (Reissert 1909), we expected *o*- and *p*-chloronitrosobenzenes to be reduced by methanolic methoxide rather than undergo chlorine replacement at normal temperatures. This has been confirmed experimentally at 30 °C; 2,2′-dichloroazoxybenzene, m.p. 56 °C (Brand 1903 gives 56 °C), and 4,4′-dichloroazoxybenzene, m.p. 158 °C (Zechmeister and Rom 1929 give 158 °C), were obtained from respective reaction mixtures.

(*d*) *Preparation of Materials*

o-Chloronitrosobenzene, prepared by reduction of the nitro-compound (Lutz and Lytton 1937), had m.p. 56 °C (lit. 56 °C).

p-Chloronitrosobenzene, obtained by oxidation of *p*-chloroaniline (Ingold 1924) or by reduction of the nitro-compound as above, had m.p. 89–90 °C (lit. 90 °C). 4-Chloro-3-nitroaniline (cf. Borsche and Exss 1923) in 55% final yield from *p*-chloroaniline treated at —5 to 0 °C with oleum (SO_3, 30%) and 100% nitric acid. The crude product was dissolved in conc. hydrochloric acid, treated with charcoal, and reprecipitated by addition of aqueous ammonia then solid sodium carbonate. It had m.p. 102–103 °C (lit. 102·5–103 °C, 17% yield).

1-Chloro-2-nitro-4-nitrosobenzene was prepared from 4-chloro-3-nitroaniline by oxidation (Ingold 1924). Washing with water, steam-distillation, and recrystallization from aqueous ethanol gave a pale yellow *nitroso-compound*, m.p. 92·5–93 °C (Found: C, 38·4; H, 1·7; N, 15·1; Cl, 19·1%. Calc. for $C_6H_3O_3N_2Cl$: C, 38·6; H, 1·6; N, 15·0; Cl, 19·0%). (M.p. 120 °C (no analysis) was reported by Brand and Eisenmenger 1913).

1-Chloro-2-nitro-4-phenylazobenzene, as Borsche and Exss (1923) obtained from ligroin as plates, m.p. 89 °C (Bunnett, Moe, and Knutson (1954) report m.p. 89–89·5 °C).

1-Chloro-2-nitro-4-α- and -β-phenylazoxybenzenes were prepared by oxidation of the azo-compound with peracetic acid (cf. Angeli 1910; Aston and Parker 1934). The more insoluble *α-compound* was precipitated, and after five recrystallizations had m.p. (constant) 127·5 °C. The acetic acid filtrate was poured into about double its volume of water, and the *β-compound* obtained impure; after four recrystallizations it had m.p. (constant) 93–94 °C. The α- and β-compounds have a mixed m.p. between those of the pure compounds as might be expected from their close relationship. The allotment of structure to the isomers was made from the known hydroxy compounds obtained from them (see below), as well as by prediction from reactivity differences.

4-Azido-1-chloro-2-nitrobenzene was prepared by keeping the diazonium solution from 4-chloro-3-nitroaniline (7·5 g) between —10 and 0 °C while sodium azide (3·8 g) in water (40 ml) was added with vigorous stirring. The white precipitate was filtered and distilled as rapidly as possible until the distillate became coloured. The solid *azido-compound* was obtained from light petroleum as light-sensitive pale brown needles, m.p. 74 °C (Found: C, 36·5; H, 1·8; N, 28·2; Cl, 18·1%. Calc. for $C_6H_3N_4Cl$: C, 36·3; H, 1·5; N, 28·2; Cl, 17·9%). The vapour of this substance appears to be very toxic; headache and heart symptoms resembling those due to hydrazoic acid.

(*e*) *Products*

(i) *4-Azido-1-methoxy-2-nitrobenzene.*—Because of decomposition of the azide group the usual isolation of an "infinity" product could not be carried out. However, this side reaction was comparatively unimportant. Therefore six aliquots, after 70% reaction (shown by Cl^- formation), were poured into water. The brown crystals obtained gave analyses corresponding to 70% of *methoxy-compound* and 30% of starting material.

Separation of the pure methoxy-compound was not attempted.

(ii) *1-Methoxy-2-nitro-4-phenylazobenzene.*—The "infinity" product had m.p. 105·5 °C (Borsche and Exss (1923) give 104–105 °C; Bunnett, Moe, and Knutson (1954) give 107 °C) (Found: C, 60·6; H, 3·9; O, 18·3%. Calc. for $C_{13}H_{11}O_3N_3$: C, 60·7; H, 4·2; O, 18·6%).

(iii) *1-Methoxy-2-nitro-4-α-phenylazoxybenzene.*—Although the solubility of the chloro-compound in methanol is inconveniently low for runs, the *methoxy-compound* was obtained using methanolic methoxide as yellow crystals, m.p. 158 °C (Found: C, 57·3; H, 4·1; O, 23·9%. Calc. for $C_{13}H_{11}O_4N_3$: C, 57·2; H, 4·1; O, 23·5%).

(iv) *1-Methoxy-2-nitro-4-β-phenylazoxybenzene.*—The "infinity" *methoxy-compound* was obtained as yellow crystals, m.p. 121–122 °C (Found: C, 57·4; H, 4·2; N, 15·4%. Calc. for $C_{13}H_{11}O_4N_3$: C, 57·2; H, 4·1; N, 15·4%).

(v) *1-Methoxy-2-nitro-4-nitrosobenzene.*—No attempt was made to isolate this compound.

(vi) *2-Nitro-4-α-phenylazoxyphenol.*—The "infinity" product had m.p. 125 °C (Angeli, Bigiavi, and Carrara (1922) give 125 °C).

(vii) *2-Nitro-4-β-phenylazoxyphenol.*—The "infinity" product had m.p. 165 °C but on recrystallization rose to 168 °C (Angeli and Bigiavi (1924) give 174 °C). Difficulties were experienced with both azoxyphenols because of contamination with silicates.

IV. Acknowledgments

The authors thank Mr. R. Bolton for preparation of 4-chloro-3-nitroaniline and 4-azido-1-chloro-2-nitrobenzene.

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MAGNETIC SUSCEPTIBILITY AND THE STRUCTURE OF TRI-COORDINATED COPPER(II) COMPLEXES

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Summary

The magnetic susceptibilities of 2-hydroxynaphthaldehyde-(1)-[2-hydroxyanil] Cu(II), 5-nitrosalicylalanthranilic acid Cu(II), 5-bromosalicylalanthranilic acid Cu(II), 2-hydroxyformazylbenzene Cu(II), and 2-carboxyformazylbenzene Cu(II), as well as their monopyridino-compounds, have been measured by the Gouy method at 25 °C. From the data of magnetic susceptibility, the effective magnetic moments were calculated per one copper atom in these chelates. Some of the pyridine-free complexes show magnetic moments that are smaller than the theoretical moment, 1·73 B.M., for one odd electron, while others have normal magnetic moments. Taking into account four other tri-coordinated copper chelates reported in a preceding paper, two alternative suggestions were made as follows. First, the subnormal moments resulting from the close distance of approach of two copper atoms in dimer molecules can be correlated with the planar configuration of chelate rings involving a copper atom. On the other hand, when a three-dimensional ring exists, the approach of two copper atoms to such a small distance as to cause an appreciable exchange effect is hindered by steric effects, resulting in the normal magnetic moment for this type of tri-coordinated complexes. Secondly, those pyridine-free tri-coordinated copper complexes showing normal moments have a carbonyl group, the oxygen atom of which may take part in the coordination about a copper atom.

I. INTRODUCTION

The present work was undertaken as part of a programme of magneto-chemical investigations on copper complexes. We have reported (Kishita, Muto, and Kubo 1957*a*, 1957*b*) that the so-called tri-coordinated copper(II) complexes show magnetic moments considerably smaller than the theoretical value predicted from the presence of one odd electron, whereas the pyridinates of these copper complexes have moments slightly greater than the theoretical spin-only moment. A possible explanation for the subnormal moments was afforded by the formation of binuclear complexes. This presumption was based on the results of paramagnetic absorption by Bleaney and Bowers (1952) as well as of complete structural determination by means of X-rays carried out by van Niekerk and Schoening (1953*a*, 1953*b*) of copper(II) acetate monohydrate, which was shown to form dimer molecules in crystals. The specific object of the present investigation was directed to the elucidation of structural factors leading to subnormal moments of tri-coordinated copper(II) complexes. For this purpose, further studies were made on the magnetic susceptibilities of a number of copper complexes of this type and their pyridinates, all of which were prepared by one of the present authors (Y.M.).

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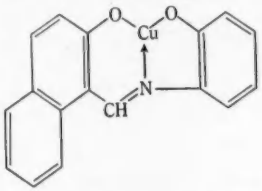
II. Preparation of Materials

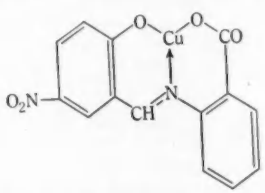
(*a*) *2-Hydroxynaphthaldehyde-(1)-[2-hydroxyanil] Cu(II)* (*Muto 1955*).—This and the following complexes were prepared by essentially the same method as that described by Kishita, Muto, and



Kubo (1957*a*, 1957*b*), namely, appropriate aldehydes were subjected to condensation with suitable amines and the resulting Schiff's bases were treated with cupric acetate, the copper atom of which replaced two hydrogen atoms of the Schiff's bases. The pyridinates were formed when water was added to the solutions of these chelates in pyridine. Pyridine could be removed from the pyridinates by heating at an appropriate temperature below 100 °C or by boiling in ethanol on a water-bath. Some of the pyridinates gradually lost pyridine when they were left to stand in air. This required special precaution.

The copper chelate is yellow-green, while its monopyridinate is brown. Both crystallize as needles (Found : Cu, 19·5 ; N, 4·4%. Calc. for $C_{17}H_{11}O_2NCu$: Cu, 19·6 ; N, 4·3%. Found : Cu, 15·7 ; N, 7·0 ; Py, 19·4%. Calc. for $C_{17}H_{11}O_2NCu.C_5H_5N$: Cu,15·7 ; N, 6·9 ; Py, 19·6%).

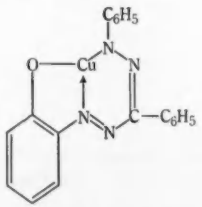
(*b*) *5-Nitrosalicylalanthranilic Acid Cu(II)* (*Muto 1955*).—The pyridine-free complex is greenish brown and the pyridinate has a bright green colour. Both form prismatic crystals (Found :



Cu, 18·2 ; N, 8·2%. Calc. for $C_{14}H_8O_5N_2Cu$: Cu, 18·3 ; N, 8·1%. Found : Cu, 14·8 ; N, 10·0 ; Py, 18·3%. Calc. for $C_{14}H_8O_5N_2Cu.C_5H_5N$: Cu, 14·9 ; N, 9·9 ; Py, 18·5%).

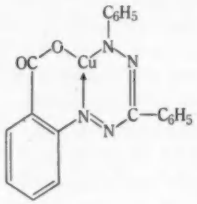
(*c*) *5-Bromosalicylalanthranilic Acid Cu(II)* (*Muto 1955*).—This compound has the same structural formula as the foregoing one, save that the nitro-group contained therein is replaced by a bromine atom. It forms greenish brown needles, while the monopyridino-compound crystallizes as bright green plates (Found : Cu, 16·9 ; N, 4·0%. Calc. for $C_{14}H_8O_3NBrCu$: Cu, 16·8 ; N, 3·7%. Found : Cu, 13·9 ; N, 6·3 ; Py, 17·4%. Calc. for $C_{14}H_8O_3NBrCu.C_5H_5N$: Cu, 13·8 ; N, 6·1 ; Py, 17·2%).

(*d*) *2-Hydroxyformazylbenzene Cu(II)* (*Wizinger and Biro 1949*).—Both the complex and its pyridinate are microcrystalline powders having an intense violet colour (Found : Cu, 16·9 ;



N, 15·0%. Calc. for $C_{19}H_{14}ON_4Cu$: Cu, 16·8; N, 14·8%. Found: Cu, 14·1; N, 15·6; Py, 17·4%. Calc. for $C_{19}H_{14}ON_4Cu.C_5H_5N$: Cu, 13·9; N, 15·3; Py, 17·3%).

(*e*) *2-Carboxyformazylbenzene Cu(II)* (*Wizinger and Biro 1949*).—Both the chelate and its pyridinate form deep violet powder crystals (Found: Cu, 15·4; N, 13·7%. Calc. for



$C_{20}H_{14}O_2N_4Cu$: Cu, 15·7; N, 13·8%. Found: Cu, 13·4; N, 14·5; Py, 16·1%. Calc. for $C_{20}H_{14}O_2N_4Cu.C_5H_5N$: Cu, 13·1; N, 14·4; Py, 16·3%).

III. Experimental Procedure and Results

The apparatus and the experimental procedure for the determination of magnetic susceptibility as well as the method of evaluation of effective magnetic moments per one atom of copper in the chelates were the same as those described in the earlier papers (Kishita, Muto, and Kubo 1957*a*, 1957*b*). The results are presented in Table 1.*

Table 1

The magnetic susceptibilities at 25 °C (per gram) and the magnetic moments of tri-coordinated copper complexes and their pyridinates

Chelates	χ (c.g.s., e.m.u.)	μ (B.M.)
2-Hydroxynaphthaldehyde-(1)-[2-hydroxyanil] Cu(II)	$2{\cdot}01\times10^{-6}$	1·39
Monopyridino-2-hydroxynaphthaldehyde-(1)-[2-hydroxyanil] Cu(II)	2·76	1·77
5-Nitrosalicylalanthranilic acid Cu(II)	3·81	1·87
Monopyridino-5-nitrosalicylalanthranilic acid Cu(II)	2·88	1·84
5-Bromosalicylalanthranilic acid Cu(II)	3·40	1·87
Monopyridino-5-bromosalicylalanthranilic acid Cu(II)	2·72	1·86
2-Hydroxyformazylbenzene Cu(II)	1·83	1·44
Monopyridino-2-hydroxyformazylbenzene Cu(II)	2·17	1·70
2-Carboxyformazylbenzene Cu(II)	2·94	1·81
Monopyridino-2-carboxyformazylbenzene Cu(II)	2·33	1·80

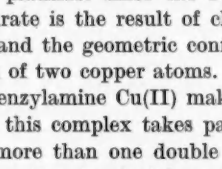
* Throughout the present paper, the data of magnetic susceptibility are given in c.g.s., e.m.u

IV. Discussion

All pyridinates studied in the present investigation have normal moments expected for cupric complexes and hence the discussions advanced in our previous paper in connexion with pyridinates are also valid in the present case.

On the other hand, it will be seen from Table 1 that some of the pyridine-free tri-coordinated copper complexes show subnormal magnetic moments while others have normal moments that are a little greater than the theoretical value of 1·73 Bohr magnetons (B.M.) for one odd electron, the excess being attributable to orbital contributions. Now, a question arises: What kind of tri-coordinated copper complexes show normal moments, or what are the structural factors leading to the subnormal values for magnetic moments? The elucidation is hampered by the difficulty of synthesizing a sufficiently wide range of tri-coordinated complexes but from the data obtained on the nine complexes so far investigated the following suggestions may be proposed.

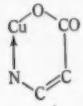
In the first place, the general characteristic of the tri-coordinated copper complexes showing normal magnetic moments seems to be the presence of a six-membered chelate ring having only one double bond, whereas in those complexes showing subnormal moments, the copper atom is involved in two rings both of which are either a five-membered ring or a six-membered one having conjugated double bonds. Unlike a five-membered ring and a six-membered ring having conjugated double bonds, both of which are planar, a six-membered ring having only one double bond has a three-dimensional structure (Sakashita 1953). Since from steric reasons, the approach of two copper atoms to such a small distance as to cause an appreciable exchange effect is hindered by the presence of a three-dimensional ring, the formation of dimers will not take place, resulting in the normal magnetic moment for this type of tri-coordinated complex. This generalization seems to be plausible since the subnormal moment found for copper(II) acetate monohydrate is the result of close proximity of two copper atoms in a dimer molecule and the geometric configuration of ligands is surely responsible for the approach of two copper atoms. One might suspect that the case of salicylal-2-hydroxybenzylamine Cu(II) makes an exception to this rule. Although a copper atom in this complex takes part in the formation of a six-membered ring having no more than one double bond, it shows a subnormal magnetic moment. However, the chemical formula as given to this molecule



is based on the synthesis of the corresponding Schiff's base. When the copper complex is formed, the one half of the molecule may be equivalent to the other half: a symmetric planar structure will result from prototropic rearrangement involving slight displacements of three hydrogen atoms. In this connexion, mention should be made of a few anomalous characters of salicylal-2-hydroxy-benzylamine complexes. For instance, the magnetic moment 0·87 B.M. of

salicylal-2-hydroxybenzylamine Cu(II) is smaller to a considerable extent than those of other copper complexes showing subnormal moments, which mostly fall in the range 1·34-1·44 B.M. Again, monopyridinosalicylal-2-hydroxybenzylamine Ni(II) was found, as will be reported in a subsequent paper, to have a magnetic moment of 2·31 B.M. instead of a moment close to the theoretical spin-only moment 2·83 ($=\sqrt{8}$) B.M. for two odd electrons, whereas pyridinates usually show normal moments.

Secondly, an entirely different possibility of explanation can be presented from the following fact. Only three pyridine-free complexes, that is, 5-nitrosalicylalanthranilic acid Cu(II), 5-bromosalicylalanthranilic acid Cu(II), and 2-carboxyformazylbenzene Cu(II) were found to show normal moments greater than 1·73 B.M. They are characterized by having a



ring, whereas the same ring system does not exist in complexes showing subnormal moments. It is not altogether inconceivable that the oxygen atom of a carbonyl group is capable of being coordinated on a copper atom belonging to the same or other monomeric molecule in such a manner that the resulting tetra-coordinated copper atom shows a normal magnetic moment (see also Bullen 1956; Shibata, Kishita, and Kubo 1957).

These two statements on the subject are conflicting and it is difficult to arrive at a conclusion. But wherever the truth lies in this debatable question, there can be no doubt that the clue to the elucidation of the problem must be sought in more extensive studies on tri-coordinated copper complexes having different types of ligand molecules. Our future investigations will be directed along this line.

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THE KINETICS OF THE PYROLYSIS OF *CYCLO*HEXYL CHLORIDE

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Summary

*cyclo*Hexyl chloride has been shown to decompose in the gas phase at 318–385 °C almost exclusively to *cyclo*hexene and hydrogen chloride. With clean glass-walled reactors the reaction was largely heterogeneous, but after the walls were coated with a carbonaceous film a homogeneous first-order reaction was found to predominate. For initial pressures within the range 4–40 cm mercury the rate coefficients for the homogeneous reaction were expressible as

$$k = 5 \cdot 88 \times 10^{13} \exp(-50{,}000 \text{ cal}/RT) \text{ sec}^{-1}.$$

There was some evidence for the rate coefficient becoming pressure-dependent below 5–10 mm initial pressure of reactant.

The reaction exhibited no induction periods and the velocity was virtually unaffected by the addition of large amounts of propene or *cyclo*hexene and traces of chlorine or bromine. The results were consistent with a unimolecular elimination of hydrogen chloride.

I. Introduction

In recent years, the kinetics of the gas-phase pyrolysis of a large number of chlorinated hydrocarbons have been described.†

In the case of many monochlorinated saturated hydrocarbons the stoicheiometry is well represented by the equation

$$C_nH_mCl \rightarrow C_nH_{m-1} + HCl,$$

small amounts only of side reactions being observed. Clean glass surfaces are known to act catalytically but it has been demonstrated (Brearley, Kistiakowsky, and Stauffer 1936 ; Barton and Howlett 1949) that by using vessels seasoned by prolonged contact with reaction products, the heterogeneous reaction can be suppressed and the homogeneous decomposition may be studied. A fine carbonaceous deposit is produced during the seasoning process, and the usefulness of this deposit may be affected by a very thorough evacuation of the flask or the admission of even small amounts of oxygen.

Barton and Onyon (1949, p. 733) suggested two possible mechanisms for the homogeneous dehydrochlorination and on the basis of these accurately predicted the mode of decomposition of a number of substances. The first

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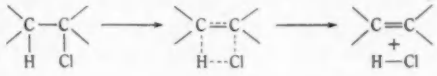
† Goodall and Howlett (1954) list all the important references up to the beginning of 1954. Since then the following important studies have been reported : Maccoll and Thomas (1955*a*) ; (see also Ingold 1957, p. 285) ; Goodall and Howlett (1956*a*, 1956*b*) ; Porter and Rust (1956).

mechanism is a direct unimolecular elimination of hydrogen chloride through a four-centre transition state requiring the presence of a hydrogen atom β to the halogen :



The second suggested mechanism is of a radical chain type probably initiated by the rupture of a C—Cl bond,

$$C_nH_mCl \rightarrow C_nH_m\cdot + Cl\cdot, \qquad \text{(initiation)}$$

$$\left.\begin{aligned} Cl\cdot + C_nH_mCl &\rightarrow (C_nH_{m-1}Cl)\cdot + HCl, \\ (C_nH_{m-1}Cl)\cdot &\rightarrow C_nH_{m-1} + Cl\cdot, \end{aligned}\right\} \qquad \text{(propagation)}$$

$$(C_nH_{m-1}Cl)\cdot + Cl\cdot \rightarrow \text{end of chain.}$$

The overall activation energy for each of these processes could be much less than that required to break the C—Cl bond.

To these should be added a third possibility, namely, a *non-chain* radical mechanism of the type discussed by Daniels and Veltman (1939) for ethyl bromide, for example,

$$C_nH_mCl \rightarrow C_nH_m\cdot + Cl\cdot,$$
$$Cl\cdot + C_nH_mCl \rightarrow (C_nH_{m-1}Cl)\cdot + HCl,$$
$$(C_nH_{m-1}Cl)\cdot + C_nH_m\cdot \rightarrow C_nH_{m-1} + C_nH_mCl.$$

For this mechanism, the activation energy should be equal to that required for the rupture of the C—Cl bond (i.e. the initial step) and for this reason, decomposition according to this scheme is much less likely (see, however, Maccoll's (1955) case of allyl bromide pyrolysis).

In the case of monochlorinated substances, unimolecular elimination of hydrogen chloride according to mechanism 1 appears to be of more universal occurrence. Radical-chain decomposition will only occur when the decomposing substance itself or the products are not active inhibitors for the chains. Maccoll and Thomas (1955*c*, p. 2447) have shown *cyclo*hexene to be a powerful inhibitor, therefore, it is reasonable to predict that *cyclo*hexyl chloride would decompose by mechanism 1.

II. Experimental

(*a*) *Reagents*

(i) cyclo*Hexyl Chloride*.—The chlorinated hydrocarbon (Hopkin and Williams) was purified by first shaking out thoroughly with concentrated sulphuric acid, washing with saturated sodium bicarbonate solution, and then with water. The product was dried over anhydrous calcium chloride and efficiently fractionated under vacuum. The sample used for kinetic study had b.p. 143 °C/760 mm and n_D^{20} 1·4627. Rodd (1953, p. 152) lists the values 143 °C and 1·4626

respectively (Found :* C, 60·7 ; H, 9·4 ; Cl, 30·3 per cent. Calc. for $C_6H_{11}Cl$: C, 60·8 ; H, 9·3 ; Cl, 29·9 per cent.).

(ii) cyclo*Hexene*.—A commercial sample of *cyclo*hexene was purified by washing thoroughly with freshly prepared ferrous sulphate solution, then with water, dried over anhydrous calcium chloride, and carefully fractionated under atmospheric pressure. The fraction boiling between 82·3 and 82·5 °C was stored over anhydrous potassium hydroxide in the dark until required for use. It had n_D^{20} 1·4452. Rodd (1953, p. 142) lists n_D 1·4450 and b.p. 83 °C/760 mm (Found :† C, 87·5 ; H, 12·1 per cent. Calc. for C_6H_{10} : C, 87·7 ; H, 12·3 per cent.).

(iii) *Propene*.—This was prepared by the dehydration of *iso*propyl alcohol with syrupy phosphoric acid-phosphorous pentoxide mixture (Davis 1928 ; Ashdown, Harris, and Armstrong 1936). The crude propene was purified by bubbling through water, sodium hydroxide solution, and calcium chloride solution. It was dried by trap-to-trap distillations through granular anhydrous calcium chloride, and finally, stored over anhydrous calcium chloride in a glass reservoir kept in a solid carbon dioxide-acetone bath.

(iv) *Bromine*.—B.D.H. laboratory reagent grade was used directly.

(v) *Chlorine*.—I.C.I. commercial grade was taken directly from the cylinder.

(vi) *Ethyl Chloride*.—B.P. anaesthetic grade (Woolwich-Elliott Chemical Company, Sydney) was used directly.

All substances (except the chlorine) were very thoroughly outgassed under vacuum before being admitted to the reaction chamber.

(*b*) *Apparatus and Experimental Technique*

The apparatus is presented diagrammatically in Figure 1. The reactions were carried out in a Pyrex glass reaction chamber 1 of approximately 350-ml capacity housed in a high temperature metal-block thermostat 2. The chamber was joined via connecting lines to a glass membrane manometer 4 and a stopcock T_1 which led to a high vacuum system. (The dead-space in the connecting lines and manometer was approximately 7 ml.)

The thermostat was constructed from a high melting aluminium alloy in the form of a cylinder 9 in. in diameter and 18 in. long with suitable recesses to accommodate the reaction flask and thermocouple 5, and the resistance thermometer (not shown on diagram) used for control purposes. Heating was provided by electrical resistance wire wound around the outside of the furnace and connected via variable transformers to the mains. The temperature at a given point within the reaction zone could be controlled to $\pm 0{\cdot}1$ °C by means of a Sunvic resistance thermometer controller type RT2. Within the region of the reactor, the temperature gradient was found to be less than 0·5 °C. Temperatures were measured with a chromel-alumel thermocouple calibrated against a rare metal couple which had been checked by the National Standards Laboratory, Sydney, and considered accurate within $\pm 0{\cdot}5$ °C.

* Analysis was made by the C.S.I.R.O. Microanalytical Laboratory.

† Analysis was made by the N.S.W. University of Technology Microanalytical Laboratory.

Since the reaction proceeds with an increase in pressure it was found convenient to follow the extent of the decomposition by means of pressure changes. Pressures were measured with a glass diaphragm gauge 4 constructed according to the directions given by Mouquin and Garman (1937) and Newton (1950). The gauge consisted of two chambers separated by a thin glass membrane the balancing side of which was silvered. The instrument was used as a null-point detector: a galvanometer lamp 6 was focused upon it and the reflected image

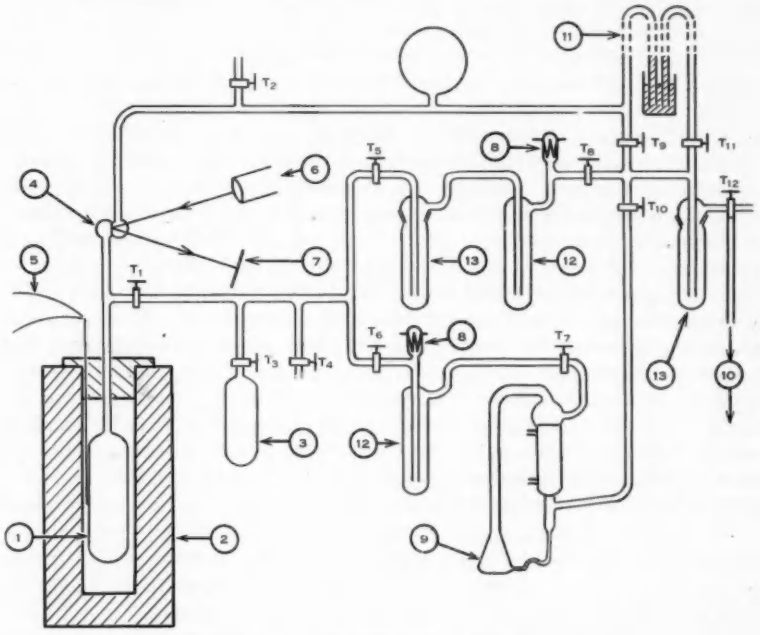


Fig. 1.—The reaction system and vacuum line.

1, Reaction vessel; 2, thermostatted furnace; 3, reactant storage reservoir; 4, glass diaphragm gauge; 5, thermocouple; 6, galvanometer lamp; 7, ground screen; 8, Pirani gauge heads; 9, mercury diffusion pump; 10, to the rotary oil pump; 11, mercury manometers; 12, liquid air traps (permanent); 13, liquid air traps (demountable); *T*, stopcocks.

of the cross-hairs viewed on a ground screen 7, deviation from the point of balance could be detected both by movement of and decrease in clarity of the image. Several gauges were constructed which had a sensitivity of approximately $\pm 0{\cdot}1$ mm and would withstand 1 atm differential pressure. Hysteresis errors (due to a differential pressure being maintained across the membrane for a prolonged period) were minimized by holding the gauge in a condition of balance for at least 1 min prior to reading the balancing pressure.

The reaction system could be evacuated to approximately 10^{-4} mm by means of a mercury diffusion pump 9 backed with a two-stage rotary oil pump 10. The efficiency of the vacuum was checked by means of Pirani gauge heads 8. All parts of the reaction system external to the furnace and all vacuum lines required for handling condensible materials were wound with resistance wire through which a current was passed for heating. Dow Corning high vacuum silicone grease was used as a stopcock lubricant.

To carry out a kinetic run, the apparatus was first completely evacuated and the diaphragm gauge zero determined. Tap T_9 was closed and air was admitted through tap T_2 to give a balancing pressure approximately equal to the anticipated initial pressure of reactant in the reaction chamber. With taps T_4, T_5, and T_6 closed, previously outgassed *cyclo*hexyl chloride was quickly distilled from the storage reservoir 3 through taps T_3 and T_1 into the reaction chamber until the diaphragm gauge was near balance. Tap T_1 was then quickly closed and a stopwatch started. The time of addition of the reactant was generally less than 5 sec and judging from the diaphragm gauge, the reactant reached the required temperature almost immediately. The pyrolysis was followed by balancing the diaphragm gauge with taps T_2 and T_9 at regular time intervals and reading the balancing pressure on the mercury manometer 11. Except in the case of runs at the higher temperatures, the initial pressure p_0 of reactant was determined by extrapolating later pressure readings back to zero time. At the conclusion of the run, T_1 was opened and the products were either allowed through T_4 for analysis or through T_5, where they were condensed in traps 13 and 12 cooled with liquid air. For runs carried out in the presence of *cyclo*hexene or propene, these substances were first admitted to the reaction chamber via T_4 and T_1 and their pressure determined after which the *cyclo*hexyl chloride was added as described before. Chlorine and bromine were added *after* the *cyclo*hexyl chloride to avoid the possibility of these substances affecting the coating on the reactor walls.

In clean-walled reactors the decomposition was erratic and extremely rapid but after allowing a film of fine carbonized material to be formed on the walls, the reaction velocity was considerably reduced and consistent results were obtained. The coating was carried out by keeping the reaction chamber in contact with decomposing ethyl chloride at 450 °C for about 10 days, during which time 50–100 fresh additions of ethyl chloride were made. Admission of traces of oxygen to the coated vessel greatly increased the rate of decomposition of *cyclo*hexyl chloride in subsequent runs. When this occurred at room temperature the effect was not permanent, the reaction velocity returning to " normal " after a few experiments, however, on one occasion when oxygen was accidentally admitted to the hot reactor, the velocity did not return to normal even after *prolonged* contact with decomposing ethyl chloride and *cyclo*hexyl chloride. On fitting a new reactor and coating as before, consistently " normal " results were obtained once more. Many workers (see, for example, Brearley, Kistiakowsky, and Stauffer 1936 ; Barton and Howlett 1949, p. 157 ; Barton and Onyon 1949, p. 726) have commented on the sensitive nature of the coating and Brearley, Kistiakowsky, and Stauffer (1936) even found " that a long or very thorough evacuation of the flask destroyed the usefulness of this carbon deposit ", although

no such effect was noted in the present study. Before the commencement of a run the reactor was evacuated with the mercury diffusion pump for approximately 1 hr at an estimated pressure of 10^{-3} to 10^{-4} mm mercury. In order to avoid accidental destruction of the coating between runs the flask was kept in constant contact with reaction products or outgassed ethyl chloride.

III. Results

(*a*) *Stoicheiometry*

As a check on the validity of the pressure changes as indicating the extent of decomposition, a series of runs were carried out at various temperatures with different percentage conversions, the products of the decomposition being distilled from the reaction vessel through T_1 and T_4 into a glass phial held at liquid air temperature. Hydrogen chloride was determined by sealing the phial, breaking the tip under water, and rinsing out the contents, after which titration was carried out with standard alkali. *cyclo*Hexene and unreacted *cyclo*hexyl chloride were identified by means of infra-red analysis* and vapour-liquid partition chromatography. For this purpose, the products of two of three runs were collected in a phial which was then held in a solid carbon dioxide-acetone bath and most of the hydrogen chloride pumped off. The analyses were carried out by comparison with " blank " mixtures of *cyclo*hexene and *cyclo*hexyl chloride made up in known proportions. The spectra of the samples and blanks of the same estimated composition were shown to be almost identical between the range 4000 to 650 cm^{-1}, however, quantitative analysis was not attempted with infra-red owing to the amount of scattered light present in the apparatus. Chromatographic separation was effected using polyethylene glycol octyl cresyl ether as a stationary phase. The apparatus was not highly efficient, however, the analysis was considered accurate to about ± 5 per cent. of the amount present. The results of these analyses are shown in Figure 2 plotted against the percentage decomposition as determined by pressure measurements. The points lie sufficiently close to the straight line of unit slope to justify the use of pressure changes as an estimate of the degree of pyrolysis.

As a further check on the stoicheiometry a number of prolonged experiments was carried out during which the reaction was allowed to approach completion. At temperatures above 334 °C, the pressure finally attained was very close to twice the initial pressure (see Table 1). At lower temperatures the final pressure was slightly less than twice the initial pressure, no doubt due to the incurrence of the reverse reaction as the addition of extra *cyclo*hexene further reduced the equilibrium decomposition (see Table 2). On the basis of these pressure measurements the equilibrium constant (K cm) for the reaction,

*cyclo*Hexyl chloride $\rightleftharpoons$ *cyclo*Hexene + hydrogen chloride,

was estimated as 166 at 325·7 °C and 90 at 317·7 °C from the experiments with *cyclo*hexyl chloride alone and 169 at 325·5 °C, 95 at 317·7 °C, and 90 at 317·6 °C from the runs with added *cyclo*hexene.

* The author is indebted to Mr. I. Reece of the N.S.W. University of Technology for the infra-red analysis.

The stability of *cyclo*hexene was tested by heating this substance by itself in a coated reactor at 367·9 °C for 91 hr. During this period the pressure increased from 8·80 to 8·90 cm only. When the pyrolysis products were pumped

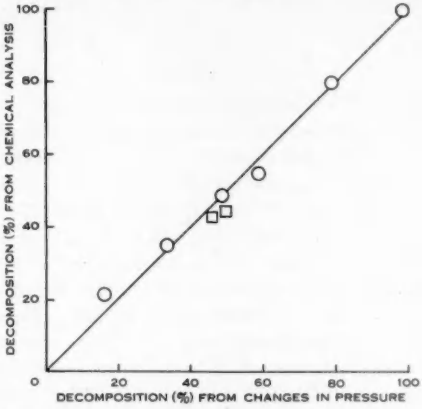


Fig. 2.—Percentage decomposition determined from pressure measurements and from chemical analysis of the products.
○ Hydrogen chloride determined by titration.
□ *cyclo*Hexene determined by gas chromatography.

off, the Pirani gauge indicated the presence of a small amount of material (probably ethylene) not completely condensed by the liquid air traps. Küchler's (1939) work on the decomposition of *cyclo*hexene provides confirmatory evidence for ignoring the secondary decomposition of *cyclo*hexene in the present study.

TABLE 1
PROLONGED PYROLYSIS OF CYCLOHEXYL CHLORIDE

Temperature (°C)	Initial Pressure, p_0 (cm)	Time (hr)	Final Pressure, p_f (cm)	p_f/p_0
350·6	10·57	23	20·92	1·98
342·1	9·88	18	19·40	1·96
334·5	17·05	20	34·02	2·00
334·5	20·54	20	40·68	1·98
334·4	2·11	20	4·17	1·98
333·8	4·84	23	4·84	1·97
325·7	20·90	74	39·68	1·90
317·7	19·71	93	36·36	1·84

(*b*) *Reaction Order and Velocity*

A series of decomposition studies in coated reactors was carried out at nine temperatures over the range 318 to 385 °C, initial pressures of *cyclo*hexyl chloride of 4 to 40 cm being used. Four typical kinetic runs are shown in Table 3.

TABLE 2

PROLONGED PYROLYSIS OF CYCLOHEXYL CHLORIDE WITH ADDED CYCLOHEXENE

Temperature (°C)	*cyclo*Hexyl Chloride-Initial Pressure, p_0 (cm)	*cyclo*Hexene Added, p_x (cm)	Time (hr)	Final Total Pressure, p_f (cm)	$(p_f-p_x)/p_0$
325·5	19·96	9·78	73	46·95	1·86
317·7	19·94	10·00	98	45·64	1·79
317·6	19·71	9·56	67	44·71	1·78

If $2p_0-p$ is the partial pressure of *cyclo*hexyl chloride at any time t, the first-order kinetic law takes the following forms:

$$dp/dt=k(2p_0-p),$$

and

$$kt=\ln [p_0/(2p_0-p)].$$

The pyrolysis was found to obey this law very closely up to at least 75 per cent. decomposition as illustrated by typical runs shown in Figure 3, the curves showing complete absence of induction periods. At 318 and 326 °C, however, there were detected very slight but definite deviations from the first-order law as the decompositions advanced, probably because the equilibrium point of the decom-

TABLE 3

DECOMPOSITION OF CYCLOHEXYL CHLORIDE

Typical kinetic runs

325·8 °C		350·2 °C		367·9 °C		385·4 °C	
t* (min)	p* (cm)	t (min)	p (cm)	t (min)	p (cm)	t (min)	p (cm)
0	9·71†	0	4·83†	0	~21·7†	0	~15†
5	9·83	2	4·94	3	23·72	2	17·62
10	9·95	5	5·07	6	25·53	4	19·70
20	10·18	10	5·29	9	27·13	6	21·40
40	10·62	20	5·74	12	28·58	8	22·81
60	11·03	30	6·14	15	29·90	10	23·98
80	11·40	40	6·46	18	31·12	12	24·93
100	11·76	50	6·78	21	32·22	14	25·73
120	12·11	60	7·05	24	33·21	16	26·37
140	12·41	70	7·32	27	34·11	18	26·90
160	12·73	80	7·55	30	34·93	20	27·34
180	13·01	90	7·75	33	35·69	22	27·70
200	13·30	100	7·95	36	36·37	24	27·99
220	13·57	110	8·12	39	36·99		
		120	8·26	42	37·55		
		130	8·39				

* t, time; p, total pressure.

† Estimated from later pressure readings.

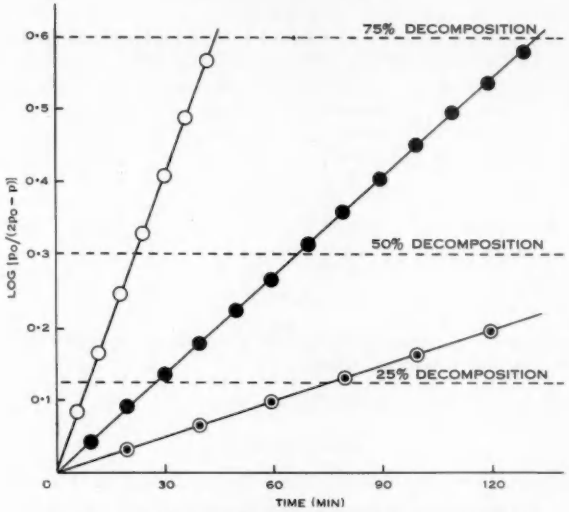


Fig. 3.—Typical first-order plots by the orthodox method.
○ $p_0 = 21 \cdot 7$ cm, temperature 367·9 °C,
● $p_0 = 4 \cdot 83$ cm, temperature 350·2 °C,
⊙ $p_0 = 15 \cdot 91$ cm, temperature 334·5 °C.

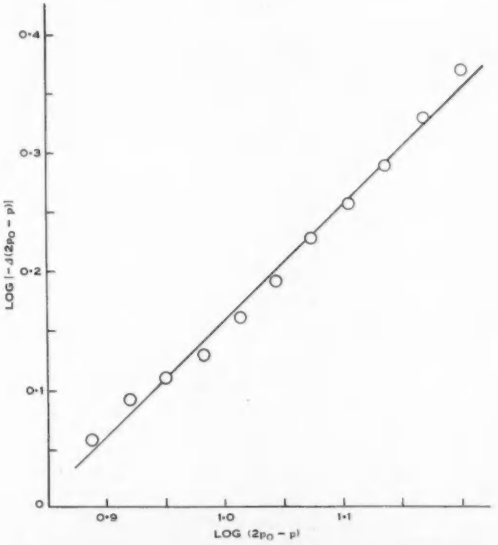


Fig. 4.—Typical log-differential plot for determination of reaction order.
$p_0 = 17 \cdot 05$ cm, temperature 334·5 °C.

positions was significantly less than 100 per cent. Further evidence for the first-order nature of the reaction was provided by graphs in which the logarithm of the pressure differences for small equal intervals of time (or alternatively,

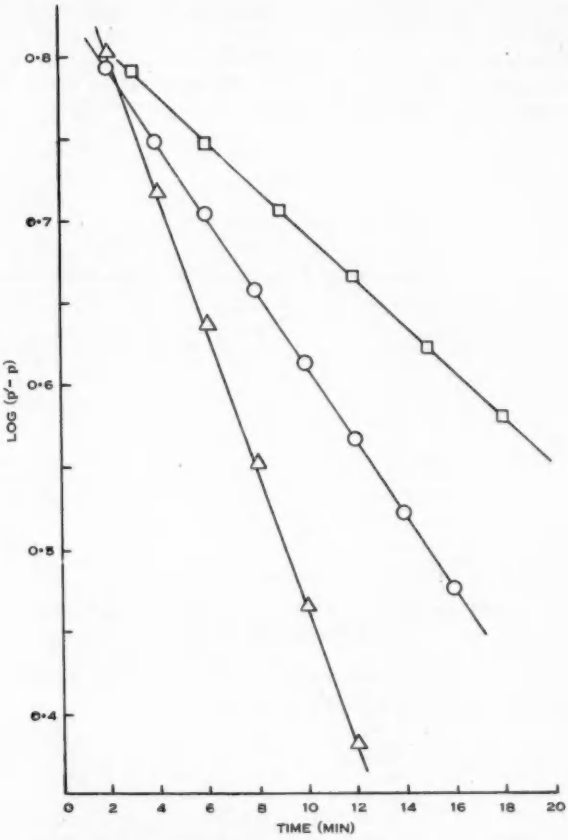


Fig. 5.—Typical first-order plots by the Guggenheim method. (The logarithms of the pressure changes, $p'-p$, for equal intervals of time, $t'-t$, are plotted against the time, t.)

□ $p_0=21\cdot7$ cm, temperature 367·9 °C, $t'-t=12$ min.
○ $p_0\sim20$ cm, temperature 376·7 °C, $t'-t=8$ min.
△ $p_0\sim15$ cm, temperature 385·4 °C, $t'-t=8$ min.

$\log[-\Delta(2p_0-p)]$) were plotted against the corresponding values of $\log(2p_0-p)$. Straight lines were obtained with slopes very close to the theoretical value of unity. An example of this type of graph is shown in Figure 4, in which the slope has been estimated as 0·99 by the method of averages.

In order to estimate numerical values for the rate coefficient k several procedures were adopted depending upon the circumstances. For runs at 334, 342, 350, and 359 °C the orthodox method was used, k being determined from the slope of graphs as in Figure 3. At 368, 377, and 385 °C, where p_0 was not known with certainty, Hartley's (1948) method of internal least squares, or Guggenheim's (1926) method (see Fig. 5) was used. Where the methods were cross-checked, excellent agreement was obtained. For example, a run at 367·9 °C in which p_0 was approximately 21·7 cm gave the following values for k: $52{\cdot}1\times10^{-5}$ (orthodox), $52{\cdot}9\times10^{-5}$ (Guggenheim), and $53{\cdot}5\times10^{-5}$ sec^{-1} (internal least

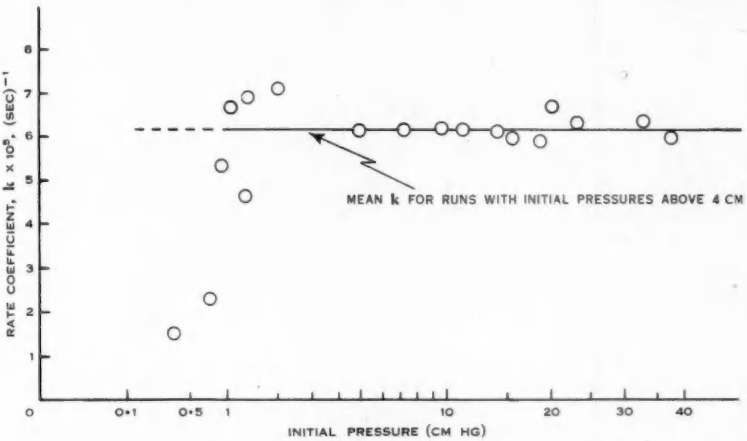


Fig. 6.—Showing the variation of reaction rate coefficient (k) with initial pressure of reactant at 334 °C.

squares). At 318 and 326 °C allowance was made for the back reaction, the following equation being used (equilibrium method):

$$(4p_0/K+1)^{\frac{1}{2}}kt=\ln\alpha+\ln\left[\frac{-1+(4p_0/K+1)^{\frac{1}{2}}}{1+(4p_0/K+1)^{\frac{1}{2}}}\right],$$

in which

$$\alpha=\frac{2(p-p_0)/K+1+(4p_0/K+1)^{\frac{1}{2}}}{-2(p-p_0)K-1+(4p_0/K+1)^{\frac{1}{2}}},$$

k was determined from the slope of the graph of $\ln\alpha$ against t (Daniels 1938, p. 77; Green and Maccoll 1955, p. 2452). However, application of the orthodox method to the initial stage of the decomposition was found to yield values of k differing by no more than 1–2 per cent. from those obtained by the equilibrium method, therefore, the former method was adopted for later calculations owing to its greater simplicity. (For example, a run at 325·6 °C in which p_0=18·04 cm gave values of k, $3{\cdot}63\times10^{-5}$ (equilibrium) and $3{\cdot}65\times10^{-5}$ sec^{-1} (orthodox up to 26 per cent. decomposition) and a run at 317·5 °C in which p_0=23·44 cm gave k, $2{\cdot}10\times10^{-5}$ (equilibrium) and $2{\cdot}12\times10^{-5}$ sec^{-1} (orthodox up to 23 per

cent. decomposition).) The least-squares method of fitting was applied in all cases where the rate coefficients were to be used for estimation of the parameters in the Arrhenius equation.

For a given temperature, the rate coefficient showed no significant variation with changes in the initial pressure of reactant within the range 4 to 40 cm.

TABLE 4

REACTION RATE COEFFICIENTS AT 334 °C

Variation with initial pressure of *cyclo*hexyl chloride

Initial Pressure (cm)	Temperature (°C)	$k \times 10^5$ (sec^{-1})	$k \times 10^{5*}$ (sec^{-1})	Initial Pressure (cm)	Temperature (°C)	$k \times 10^5$ (sec^{-1})	$k \times 10^{5*}$ (sec^{-1})
37·9	334·0	5·99	5·99	6·68	334·6	6·39	6·12
33·0	334·6	6·60	6·33	4·85	333·8	6·07	6·16
23·43	333·9	6·19	6·23	2·11	334·4	7·30†	7·10
20·54	334·5	6·89	6·65	1·37	334·4	7·11†	6·92
19·09	333·8	5·82	5·90	1·29	334·5	4·81†	4·65
15·91	334·5	6·19	5·98	1·05	334·5	6·89†	6·66
14·45	334·0	6·10	6·10	0·93	334·6	5·52†	5·29
11·22	334·5	6·28	6·06	0·73	334·4	2·27†	2·21
9·77	334·0	6·21	6·21	0·38	334·4	1·57†	1·53

* Corrected to 334·0 °C.

† Not used in the estimation of the parameters in the Arrhenius equation.

TABLE 5

RATE COEFFICIENTS AT DIFFERENT TEMPERATURES

Temperature (°C)	Number of Runs	Mean Rate Coefficient $\bar{k} \times 10^5$ (sec^{-1})	90 Per Cent. Confidence Limits $\times 10^5$ (sec^{-1})
318	9	2·06	±0·17
326	10	3·53	±0·28
334	11	6·16	±0·11
342	9	9·50	±0·34
350	8	16·70	±0·45
359	4	31·1	±0·5
368	5	54·7	±1·7
377	10	93·7	±1·8
385	8	155·9	±1·7

This may be observed from the series of runs grouped around 334 °C listed in Table 4 or from Figure 6 in which the corresponding values of k corrected by means of the Arrhenius equation to a temperature of 334·0 °C have been plotted against the initial pressure. Some runs were made at lower pressures,* and

* These were not used in the estimation of the parameters in the Arrhenius equation.

although the results of these were rather scattered (due to the insensitivity of the membrane gauge used) there appeared to be some evidence of the rate coefficient becoming pressure-dependent below 5–10 mm initial pressure of reactant.

Table 5 shows the arithmetic mean values of k together with the corresponding 90 per cent. confidence limits at nine different temperatures.* The plot of log k against $1/T$ is shown in Figure 7.

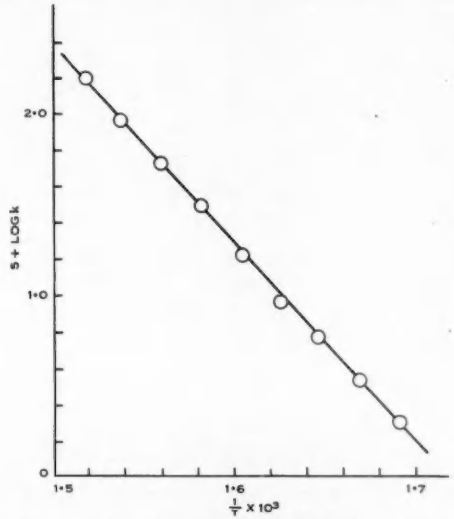


Fig. 7.—The Arrhenius plot. The points shown correspond to mean rate coefficients as listed in Table 5.

The constants A and E in the Arrhenius equation $k=A\exp(-E/RT)$ were estimated from the best straight line of log k plotted against $1/T$ by the least-squares procedure. In this calculation the same statistical weight was given to each of the 74 *originally* observed rate coefficients, and it was assumed that all errors resided in the log k values and none in the temperature measurements. The results together with the corresponding 90 per cent. confidence limits are

$$E=49\cdot98\pm0\cdot57 \text{ kcal},$$

$$\log_{10}A=13\cdot77\pm0\cdot20,$$

that is,

$$A=5\cdot9\times10^{13} \text{ sec}^{-1}.$$

* The original values of k may have corresponded to temperatures slightly different from those shown in Table 5 and accordingly these values have been adjusted to the temperatures listed by means of the Arrhenius equation.

(c) *Effects of Added Substances*

Pyrolyses carried out in the presence of added substances are shown in Table 6. By comparing the rate coefficients with those listed in Table 5, it may be observed that the rate of decomposition of *cyclo*hexyl chloride was virtually unaffected by the presence of large amounts of *cyclo*hexene, propene, or ethyl chloride* and small amounts of bromine or chlorine.

TABLE 6

EFFECTS OF ADDED SUBSTANCES

Added Substance	Temperature (°C)	Initial Pressure of *cyclo*Hexyl Chloride (cm)	Initial Pressure of Added Substance (cm)	Pyrolysis Rate* $k \times 10^5$ (sec^{-1})
*cyclo*Hexene ..	318	20·0	10·0	2·06
	318	10·8	10·1	2·61
	326	9·9	9·9	4·26
	334	6·8	10·2	6·18
	334	12·3	10·3	6·20
	334	15·0	10·1	6·05
	334	24·8	10·1	5·86
	342	9·2	11·1	10·81
Propene ..	334	5·4	9·9	6·41
	334	10·0	10·4	6·45
	334	15·1	9·7	6·00
	334	19·7	9·9	5·88
Ethyl chloride	342	24·8	9·9	9·57
Bromine ..	342	10·2	0·6	10·16
	342	10·0	0·8	9·64
Chlorine ..	342	19·4	1·3	8·65

* These have been adjusted slightly for temperature as explained previously (see Table 4).

A number of runs was made in a reaction vessel which had been packed with Pyrex glass tubes and coated by prolonged contact with decomposing ethyl chloride as described previously. The velocity of decomposition of *cyclo*hexyl chloride in this vessel (surface area : volume = 11·5 cm^{-1}) was found to be very little different from that observed in the normal vessel (surface area : volume = 0·84 cm^{-1}) as may be seen by comparison of Table 7 with Table 5. Constants E and log A in the Arrhenius equation together with the 90 per cent.

* Ethyl chloride was tested because it was used for the coating of the reactor walls.

confidence limits estimated by the least-squares procedure for runs in the packed reactor were as follows:

$$E = 50 \cdot 3 \pm 2 \cdot 8 \text{ kcal},$$
$$\log_{10} A = 13 \cdot 9 \pm 1 \cdot 0,$$

that is,

$$A = 8 \times 10^{13} \text{ sec}^{-1}.$$

From these results it was concluded that in coated reaction vessels the decompositions studied were almost entirely homogeneous.

TABLE 7

PYROLYSES IN A PACKED REACTOR

Temperature (°C)	Initial Pressure of *cyclo*Hexyl Chloride (cm)	Pyrolysis Rate* $k \times 10^5$ (sec^{-1})	Temperature (°C)	Initial Pressure of *cyclo*Hexyl Chloride (cm)	Pyrolysis Rate* $k \times 10^5$ (sec^{-1})
318	20·3	2·29	350	19·5	16·2
326	20·0	3·79	359	19·7	32·1
334	20·0	5·97	368	19·6	67·4
342	19·5	11·80	377	19·7	101·5

* Values adjusted slightly for temperature (see Table 4).

IV. Discussion

It has been shown that *cyclo*hexyl chloride pyrolyses in " seasoned " reaction vessels by a homogeneous first-order reaction to yield *cyclo*hexene and hydrogen chloride. No induction periods were observed and the addition of *cyclo*hexene and propene caused no appreciable change in the reaction velocity. As these substances are well known as radical-chain inhibitors (Rice and Polly 1938; Maccoll and Thomas 1955*c*, p. 2447) it must be concluded that these chains play little or no part in the decomposition within the temperature range studied. In addition, a chain reaction could not be initiated by the addition of small amounts of bromine or chlorine. These results are consistent with a unimolecular elimination of hydrogen chloride through a four-centre transition state as discussed under mechanism 1 (Section I). The non-exponential term A of the Arrhenius equation was estimated as $5 \cdot 9 \times 10^{13}$ sec^{-1} which is a value considered as normal for a unimolecular reaction (Glasstone, Laidler, and Eyring 1941, pp. 295–7). The non-chain radical mechanism has been ruled out on the grounds of the experimental activation energy, 50 kcal, being much smaller than the energy of homolytic rupture of a secondary C—Cl bond (about 82 cal; Lane, Linnett, and Oswin 1953).

It is interesting to compare this activation energy with values found for other secondary monohalogenated hydrocarbons decomposing in the gas phase by a similar mechanism. Barton, Head, and Williams (1952) studied the

pyrolysis of (−)-menthyl chloride by a combination of both static and dynamic methods and reported an activation energy of 45 kcal. For the pyrolysis of 2-chloropropane, Barton and Head (1950) recorded a value of 50·5 kcal, the technique used being similar to the one described in the present study. No other comprehensive studies of this type upon secondary monochlorinated hydrocarbons appear to have been made. However, by comparison with the recorded values of 46·1 kcal for *cyclo*hexyl bromide (Green and Maccoll 1955) and 47·8 kcal for 2-bromopropane (Maccoll and Thomas 1955*b*) it seems that the activation energy reported for (−)-menthyl chloride could be slightly low. Other values recorded for the bromides are 43·8 kcal for secondary butyl bromide (Maccoll and Thomas 1955*c*) and 41·4 kcal for *cyclo*pentyl bromide (Price, Shaw, and Trotman-Dickenson 1956).* The pyrolysis of the iodides generally proceeds by a much more complex mechanism (Holmes and Maccoll 1957).

Assuming that the reaction rate coefficients at 334 °C for the dehydrochlorination of *cyclo*hexyl chloride became pressure-dependent below 5–10 mm initial pressure of reactant it is possible, by the method of Hinshelwood (1940, p. 79), to obtain an estimate of the number of " classical oscillators " within an activated molecule contributing towards the decomposition. For this purpose it is necessary to know the effective collision diameter of the molecule. This has been set at 6·0 Å from a study of molecular models (Courtaulds-van der Waals radii) and a comparison under corresponding conditions of the density of the liquid with other liquids of known molecular collision diameter. On the basis of these values, the number of classical oscillators has been estimated as 10. A careful study of the low pressure decomposition of four chlorinated hydrocarbons has been made by Howlett (1952*a*, 1952*b*), who has reported the following values for the number of classical oscillators as estimated† by the Hinshelwood method :

12 for 1,2-dichloroethane	6–7 for 1,1-dichloroethane
13–14 for ethyl chloride	12 for 2-chloropropane

In spite of the flimsy evidence in the case of *cyclo*hexyl chloride the agreement with these values is very satisfactory.

V. Acknowledgments

The author wishes to record his gratitude to Dr. M. F. R. Mulcahy, Department of Chemistry, University of Melbourne, for helpful discussion of the results, and Mr. P. D. Lark, Department of Chemistry, N.S.W. University of Technology, for advice on statistical methods. Thanks are also due to Professor D. P. Mellor, Department of Chemistry, N.S.W. University of Technology, and to Dr. A. Maccoll, Reader in Chemistry, University College, London, for their continued interest.

* The author is at present engaged upon a study of the pyrolysis of *cyclo*pentyl chloride.

† No allowance appears to have been made in these calculations for the number of *translational* degrees of freedom. Consideration of this would reduce Howlett's values by unity.

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THE OCCURRENCE OF PARAMAGNETIC AND DIAMAGNETIC ISOMERS OF BIS(*N*-METHYLSALICYLALDIMINE)NICKEL(II)

By C. M. Harris,* S. L. Lenzer,* and R. L. Martin*

[*Manuscript received March* 26, 1958]

Summary

The isolation of a stable well-defined paramagnetic isomer of bis(*N*-methylsalicylaldimine)nickel(II) is reported. This buff coloured compound has a magnetic moment at room temperature of 3·2 B.M., corresponding to the presence of two unpaired spins/Ni atom, and is insoluble in a large variety of solvents in marked contrast to the soluble green diamagnetic isomer. The magnetic moment is nearly independent of temperature in the range 115–350 °K, and probably has its origin in a polymeric, and hence insoluble, octahedral structure involving $4s4p^34d^2$ nickel-bonding orbitals.

I. Introduction

Nearly 20 years have elapsed since Klemm and Raddatz (1942) first reported the isolation of two forms of the compound bis(*N*-methylsalicylaldimine)nickel(II). In the solid state, one form was diamagnetic while the other, which was paramagnetic, reverted to the diamagnetic modification on standing in air. Although convinced of the existence of this green paramagnetic isomer, Klemm and Raddatz were unable to repeat successfully or to formulate experimental conditions for its preparation.

The green diamagnetic form of this complex was subsequently shown by Willis and Mellor (1947) to develop some paramagnetism in benzene and chloroform solutions. The room temperature moments in these solvents lay in the range 2·2–2·4 Bohr magnetons (B.M.), and led them to postulate the existence of an equilibrium between square ($3d4s4p^2$) diamagnetic and tetrahedral ($4s4p^3$) paramagnetic forms. They further observed that the moment rose to 3·2 B.M. in pyridine solution, which they ascribed to the formation of a bispyridine octahedral complex employing $4s4p^34d^2$ bonds. Confirmation of this last proposal resulted from the isolation of the pyridine adduct first by Basolo and Matoush (1953) and later by Clark and Odell (1955).

The present authors have now succeeded in transforming the soluble monomeric diamagnetic form of bis(*N*-methylsalicylaldimine)nickel(II) into a stable paramagnetic isomer ($\mu = 3 \cdot 2$ B.M./Ni atom) by heating it either in biphenyl, or in the solid state, to temperatures in the range 150–200 °C. The dark green diamagnetic form changes to a buff coloured powder. There is no loss in weight, and the resulting compound has the same analysis as the diamagnetic form. The magnetic susceptibility obeys a Curie-Weiss law (with $\theta = 20°$) in the temperature range 115–350 °K, so that the magnetic moment is

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nearly independent of temperature (see Fig. 1). Unlike the diamagnetic isomer, the paramagnetic form displays a marked insolubility in a large variety of polar and non-polar solvents including strong donor solvents such as pyridine. This paramagnetic compound bears little resemblance to the green paramagnetic isomer, accidentally prepared by Klemm and Raddatz (loc. cit.), for it is stable in air and differs markedly in colour.

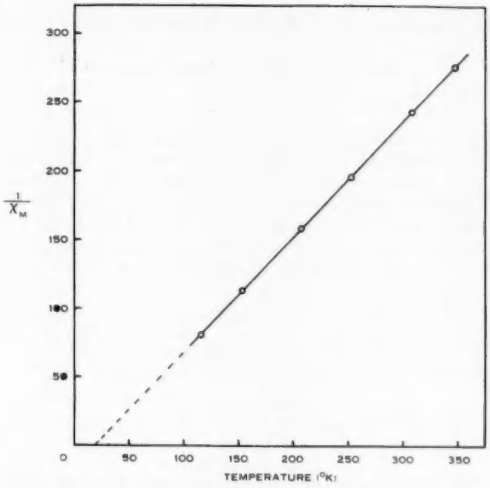

Fig. 1.—Reciprocal molar susceptibility of paramagnetic isomer of bis(*N*-methylsalicylaldimine)nickel(II) as a function of temperature.

The paramagnetism of this new isomer of bis(*N*-methylsalicylaldimine) nickel(II) can be interpreted in terms of at least three possible bonding arrangements :

(i) $4s4p^3$-bonding involving a mononuclear, tetrahedral structure ;
(ii) $4s4p^24d$-bonding involving a mononuclear square structure ; or
(iii) $4s4p^34d^2$-bonding involving a six-covalent polymeric structure.

It is interesting to note that although the existence of tetrahedral nickel(II) compounds has frequently been postulated, there are, to our knowledge,* no nickel(II) complexes which have been shown to possess this configuration by a complete X-ray structural determination. The complete insolubility of the paramagnetic isomer, reported in the present paper, is not in keeping with a mononuclear four-covalent structure, particularly in view of the solubility of the green diamagnetic square isomer, which is monomeric, and also soluble in a large number of organic solvents.

* Since this paper was submitted for publication, Venanzi (*J. Chem. Soc.* **1958** : 719) has reported that bis(triphenylphosphine)nickel(II) halides, $(Ph_3P)_2NiX_2$, are examples of sterically forced tetrahedral configurations of bivalent nickel.

Recently Sacconi, Paoletti, and Del Re (1957) have modified Willis and Mellor's (1947) proposal to explain the partial paramagnetism, exhibited by several diamagnetic *N*-alkylsalicylaldimine complexes of nickel(II), in solution. They have interpreted the diamagnetic-paramagnetic equilibrium in terms of the coexistence of "low spin" square ($3d4s4p^2$) and "high spin" square ($4s4p^24d$) isomers. However, both the temperature independence of the magnetic moment of our paramagnetic isomer, and the persistent diamagnetism of the green isomer, in the range 100–350 °K, preclude a similar interpretation for the two solid forms obtained in the present work.

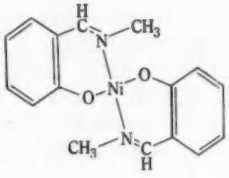

Fig. 2

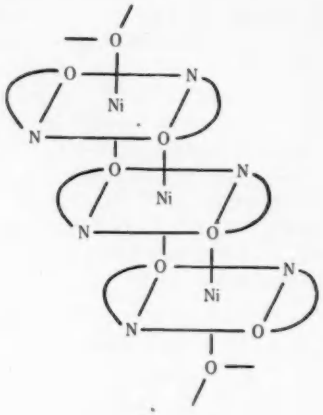

Fig. 3

Fig. 2.—Structural formula of the green diamagnetic planar molecule, bis(*N*-methylsalicylaldimine)nickel(II).

Fig. 3.—Proposed polymeric octahedral structure for the buff coloured paramagnetic isomer of bis(*N*-methylsalicylaldimine)nickel(II).

The present results can be better understood by formulating the paramagnetic isomer as a polymeric six-covalent structure involving $4s4p^34d^2$-bonding. Such an arrangement could readily occur in the present compound by oxygen atoms from adjacent square molecules (Fig. 2), completing a polymeric, six-covalent arrangement about the nickel atom as shown diagrammatically in Figure 3. Such an arrangement would necessitate three-covalent oxygen atoms which are, of course, well established in such compounds as hydroxonium perchlorate, boron trifluoride addition compounds of oxygen-containing ligands, and a great number of covalently aquated metal ions such as $[Cr(H_2O)_6]^{+++}$. It is interesting to note that Dimaras (1957) has recently examined anhydrous nickel(II) sulphate by X-rays and has found it to have a polymeric structure with nickel at the centre of a slightly distorted octahedron of oxygen atoms.

The tendency for diamagnetic bis(*N*-alkylsalicylaldimine)nickel(II) complexes to adopt a paramagnetic six-covalent configuration is further reflected by their ready reaction with 1,10-phenanthroline in benzene solution. Light

green addition complexes of the general formula, [Ni(*N*-alkylsalicylaldimine)$_2$-phen], where alkyl=methyl, ethyl, and benzyl, were readily prepared, and possessed magnetic moments, μ=3·2 B.M./Ni atom (Harris, Lenzer, and Martin 1957, unpublished data). In these molecules, unlike the bispyridine type adducts mentioned previously, the two salicylaldimine chelates can no longer occupy a square planar arrangement about nickel, due to the rigid nature of the phenanthroline molecule which must occupy *cis*-octahedral positions. Attempts to convert other diamagnetic (*N*-alkylsalicylaldimine)nickel(II) derivatives to paramagnetic forms have so far been unsuccessful.

II. Experimental

(*a*) *Bis*(N-*methylsalicylaldimine*)*nickel*(*II*)

(i) *The Diamagnetic Form.*—This compound was prepared by the method of Klemm and Raddatz (1942) and purified by recrystallization from hot chloroform. The dark green crystals were dried under vacuum over phosphoric oxide (Found: C, 58·7; H, 4·8; N, 8·7%; *M* (ebullioscopically in benzene) 1·0% solution, 305; 1·5% solution, 293; (cryoscopically in 0·6% benzene solution), 358. Calc. for $C_{16}H_{16}O_2N_2Ni$: C, 58·8; H, 4·9; N, 8·6%; *M*, 327). The compound was not recrystallized from pyridine as suggested by Klemm and Raddatz (loc. cit.) as this yields a paramagnetic bispyridine adduct (see Basolo and Matoush 1953).

Table 1

Temperature (°C)	Time (hr)	Magnetic Moments at Room Temp. (B.M./Ni atom)
150–160	6	3·11
200	0·5	3·33
200	2	3·19
Mean:		3·21

(ii) *The Paramagnetic Form.*—This compound was prepared from the diamagnetic isomer by heating in two ways:

(1) *By Heating in the Solid State.* The diamagnetic isomer was transformed by heating the solid to temperatures in the range 150–200 °C for various periods of time. The temperature, time, and moments, for typical runs are shown in Table 1. The dark green crystalline compound changed to a buff powder without loss in weight (Found: C, 58·6; H, 4·9; N, 8·5%). This paramagnetic form, unlike the diamagnetic isomer, was insoluble in a large range of polar and non-polar solvents including hot pyridine.

(2) *By Heating in Biphenyl.* The same buff paramagnetic isomer was obtained by heating a mixture of 0·003 mole of biphenyl and 0·001 mole of the diamagnetic isomer in a sealed tube at 150–180 °C for 15–20 min. The green colour of the melt became lighter, and after cooling and grinding the melt, the

moment of the mixture was found to correspond to 3·20 B.M./Ni atom. The biphenyl could be removed by washing with organic solvents, leaving the buff paramagnetic isomer.

(iii) *Magnetic Measurements.*—These were made on powdered samples, at two different field strengths, using the Gouy method in conjunction with a liquid-air cryostat. No evidence was obtained for dependence of magnetic susceptibility upon the strength of the magnetic field. The gram susceptibility, χ_g, the molar susceptibility, χ_M (corrected for the underlying diamagnetism of all atoms, $\Delta = -79 \times 10^{-6}$), and the magnetic moment μ are set out in Table 2. This last quantity has been calculated both on the basis of a simple Curie law, $\mu = 2{\cdot}839[\chi_M.T]^{0{\cdot}5}$, and according to a Curie-Weiss law, $\mu = 2{\cdot}839[\chi_M.(T-20)]^{0{\cdot}5}$.

TABLE 2

MAGNETIC MEASUREMENTS

Isomer	T (°K)	$10^6 \times \chi_g$	$10^6 \times \chi_M$	μ (B.M.)	
				$\theta = 0°$	$\theta = 20°$
Green diamagnetic	102·0	−0·0842	−28	0	0
	291·0	−0·0788	−26	0	0
Buff paramagnetic	115·5	+37·68	+12400	3·40	3·09$_6$
	154·0	26·88	8867	3·32	3·09$_5$
	207·0	19·09	6320	3·25	3·09$_6$
	252·5	15·40	5114	3·23	3·09$_5$
	308·0	12·37	4123	3·20	3·09$_5$
	347·5	10·85	3626	3·19	3·09$_5$

III. ACKNOWLEDGMENTS

The authors thank Dr. E. Challen, N.S.W. University of Technology, for the microanalytical determination of carbon, hydrogen, and nitrogen.

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REACTIONS OF AROYL PEROXIDES*

IV. BENZOYL PEROXIDE WITH SOME HALIDES AND OXYHALIDES OF PHOSPHORUS AND SULPHUR

By MARGARITA KARELSKY†‡ and K. H. PAUSACKER†

[*Manuscript received April* 11, 1958]

Summary

When benzoyl peroxide was heated with phosphorus trichloride (1 and 2 mol) in benzene, or chlorobenzene solution, carbon dioxide, benzoyl chloride, and phenyl phosphonyl chloride were the major products. Diphenyl phosphonyl chloride was also formed in small yield. *p*-Chlorobenzoyl peroxide reacted with phosphorus trichloride, in benzene solution, yielding carbon dioxide, *p*-chlorobenzoyl chloride, *p*-chlorophenyl phosphonyl chloride, and *p*-chlorobenzoic anhydride. The reaction of benzoyl peroxide with phosphorus trichloride alone yielded benzoyl chloride only. Phosphorus oxychloride, on the other hand, does not enter into the reaction.

Thionyl chloride, in benzene, gave a complex mixture consisting of carbon dioxide, chlorobenzene, benzoyl chloride, phenyl benzoate, benzene sulphonyl chloride, diphenyl, and benzoic anhydride. Sulphuryl chloride in benzene yielded a mixture of carbon dioxide, chlorobenzene, benzoic acid, phenyl benzoate, and diphenyl.

The mechanisms of these various reactions are discussed.

I. INTRODUCTION

It is well known that benzoyl peroxide reacts with benzene (cf. Lynch and Pausacker 1957*a*) to give carbon dioxide (1·35 mol),§ benzoic acid (0·45 mol), and diphenyl (0·40 mol) as well as a number of other minor products, but the addition of the halides and oxyhalides of certain elements causes the reaction to take a different course. When more than 1 mole of aluminium trichloride was added to the reaction mixture, phenyl benzoate and carbon dioxide were formed in almost theoretical yield according to the equation

$$(PhCO_2)_2 + AlCl_3 \rightarrow PhCO_2Ph.AlCl_3 + CO_2$$

(Boeseken and Reynhart 1926). The addition of smaller amounts of aluminium trichloride (0·32 mol) gave lower yields of phenyl benzoate (0·26 mol) and appreciable amounts of diphenyl (0·25 mol) (Gelissen and Hermans 1925). Reynhart (1927) has found that benzoyl peroxide, in light petroleum solution, is almost quantitatively converted into phenyl benzoate and carbon dioxide in

* For Part III of this series see Lynch and Pausacker (1957*b*).

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‡ This paper represents part of a dissertation submitted in partial fulfilment of the requirements for the degree of Master of Science in the University of Melbourne.

§ Throughout the paper, mol of either reagent or product refers to mol per mol of benzoyl peroxide.

the presence of antimony pentachloride. When phosphorus pentachloride is substituted for antimony pentachloride in the above system, carbon dioxide (0·5 mol) and benzoyl chloride (1·1 mol) were the only products isolated. By heating benzoyl peroxide with phosphorus pentachloride alone, Reynhart (1927) isolated carbon dioxide (*c.* 1·0 mol), chlorobenzene (0·68 mol), benzoyl chloride (0·93 mol), and phosphorus oxychloride (1·14 mol). The principal reaction may be written as

$$(PhCO_2)_2+PCl_5 \rightarrow CO_2+PhCl+PhCOCl+POCl_3.$$

Phosphorus oxychloride did not enter into the reaction but phosphorus oxybromide gave a small yield of bromobenzene (0·13 mol). A number of other halides, including antimony pentachloride, ferric chloride, antimony trichloride, and zinc chloride, have also been added to the benzoyl peroxide-benzene system (Gelissen and Hermans 1925; Boeseken and Reynhart 1926) but conclusive results were not obtained. When stannous chloride is refluxed with benzoyl peroxide in benzene solution, virtually no carbon dioxide is evolved and the principal product is $SnCl_2(OCOPh)_2$. Antimony trichloride is also probably converted into $SbCl_3(OCOPh)_2$ (Razuvaev *et al.* 1954). Sulphuryl chloride is also effective in altering the course of the reaction which proceeds mainly according to the equation

$$(PhCO_2)_2+SO_2Cl_2 \rightarrow 2PhCl+SO_2+2CO_2$$

(Kharasch and Brown 1939).

As it is apparent that the addition of many of these reagents can radically alter the course of the benzoyl peroxide-benzene reaction, the effect of certain halides and oxyhalides of phosphorus and sulphur have been investigated in detail.

II. Experimental

Analyses were made by the C.S.I.R.O. Microanalytical Laboratory.

(*a*) *Reagents*

Most reagents were purified by the methods used by Lynch and Pausacker (1957*a*), other materials were freshly distilled before use.

(*b*) *General Procedure*

Reactions were carried out in the apparatus already described (Lynch and Pausacker 1957*a*) except that acidified silver nitrate (for hydrogen chloride), acidified potassium dichromate (for sulphur dioxide), and calcium chloride traps were placed between the reaction vessel and the gas-burette whenever appropriate.

(*c*) *Results*

(i) *Reaction of Benzoyl Peroxide with Phosphorus Trichloride.*—The reaction products were isolated by fractional distillation of the residue remaining after excess phosphorus trichloride and benzene had been removed. Benzoyl chloride, b.p. 92 °C/20 mm, benzene phosphonyl chloride, b.p. 110 °C/0·5 mm, and diphenyl phosphonyl chloride, b.p. 176 °C/0·8 mm, were obtained. Control experiments

showed that the recovery of benzoyl chloride was only 90 per cent. These three halides were identified by hydrolysis to the corresponding acid: Benzoic acid, m.p. (and mixed m.p. with an authentic sample) 122 °C; phenylphosphonic acid, m.p. (and mixed m.p. with an authentic sample kindly supplied by Dr. Leon D. Freedman) 163 °C; diphenylphosphonic acid, m.p. 193 °C (Found: C, 65·6; H, 5·1 per cent. Calc. for $C_{12}H_{11}O_2P$: C, 66·1; H, 5·2 per cent.). Michaelis and Wegner (1915) quote m.p. 195 °C for this compound.

The results are shown in Table 1. The yields of all products, and any figures in parentheses, are expressed in terms of mol per mol of benzoyl peroxide, in Tables 1 and 2.

TABLE 1

REACTION OF BENZOYL PEROXIDE WITH PHOSPHORUS TRICHLORIDE

$(PhCO_2)_2$ (g) ..	10·5	10·5	10·5	7
PhH (ml)	300	300	—	—
PhCl (ml)	—	—	300	—
PCl_3 (ml)	3·8 (1·00)	7·6 (2·00)	7·6	30
Temperature (°C) ..	78	78	100	76
CO_2	0·87, —	0·89, 0·95	1·32, 1·26	—
Ph.COCl	0·84, 0·73	0·86, 0·88	0·74, 0·68	2·02
$Ph.POCl_2$	0·68, 0·68	0·71, 0·77	0·85, 0·83	—
Ph_2POCl	0·10, 0·12	0·06, 0·04	0·11, 0·12	—
High-boiling residue (g)	0·65,* 1·16	0·62, 0·47	0·41, 0·28	—

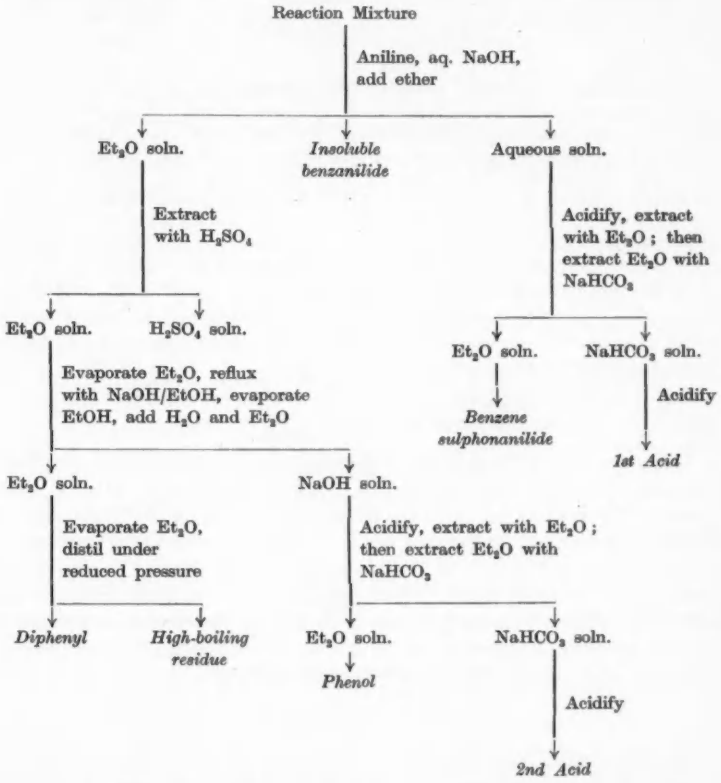
* Found: C, 72·7; H, 6·7; O, 10·2; Cl, 5·6; P, 4·8%.

(ii) *Reaction of* p-*Chlorobenzoyl Peroxide with Phosphorus Trichloride.*—Benzene (150 ml), *p*-chlorobenzoyl peroxide (4·5 g), and phosphorus trichloride (7·6 ml) were heated for 8 hr at 78 °C. Carbon dioxide (1·02 mol) was evolved and *p*-chlorobenzoic anhydride (0·26, 0·20 mol) deposited when the reaction mixture was cooled. This was filtered and the filtrate was distilled. *p*-Chlorobenzoyl chloride (0·86, 0·98 mol, b.p. 100 °C/2·0 mm) and *p*-chlorobenzene phosphonyl chloride (0·28, 0·44 mol; b.p. 115–120 °C/0·8 mm) were isolated. *p*-Chlorobenzoic anhydride crystallized from benzene, m.p. 194 °C (Found: C, 57·2; H, 3·1; Cl, 24·2 per cent. Calc. for $C_{14}H_8Cl_2O_3$: C, 56·9; H, 2·7; Cl, 24·1 per cent.). *p*-Chlorobenzoic acid (m.p. and mixed m.p. with an authentic sample 236 °C) was formed by hydrolysis of both *p*-chlorobenzoic anhydride and *p*-chlorobenzoyl chloride. *p*-Chlorobenzene phosphonyl chloride was hydrolysed to form *p*-chlorobenzenephosphonic acid, m.p. 184 °C (Found: C, 37·5; H, 3·3 per cent. Calc. for $C_6H_6ClO_3P$: C, 37·4; H, 3·1 per cent.). Kosolapoff (1947) has stated that this compound has m.p. 188 °C.

(iii) *Reaction of Benzene with Benzoyl Peroxide in the Presence of Phosphorus Oxychloride.*—Benzoyl peroxide (7 g), benzene (300 ml), and phosphorus oxychloride (5·3 ml; 2·00 mol) were heated at 78 °C for 8 hr. The reaction mixture was worked up by the general procedure given by Lynch and Pausacker (1957*a*) when the following products were isolated: carbon dioxide (0·89, 1·08 mol), 1st benzoic acid (0·57, 0·65 mol), 2nd benzoic acid (0·59, 0·60 mol), phenol (0·12, 0·10 mol), diphenyl (0·30, 0·37 mol), residue (0·99, 0·59 g).

(iv) *Reaction of Benzoyl Peroxide with Thionyl Chloride.*—After the reaction had ended, excess thionyl chloride and benzene were first distilled and then chlorobenzene (b.p. 132 °C) and benzoyl chloride (b.p. 92 °C/20 mm) were removed. Chlorobenzene was identified by conversion to 2,4-dinitrochlorobenzene (m.p. and mixed m.p. with an authentic specimen, 52 °C), and benzoyl chloride was hydrolysed to benzoic acid.

The residue was shaken with aniline (4 ml) and 2·5N sodium hydroxide solution (30 ml) for 10 min and the various products (identified by mixed m.p. with an authentic specimen) were separated as shown in the following flow sheet :



Benzoic acid could not be extracted by sodium bicarbonate from the original reaction mixture dissolved in ether and so it is therefore assumed that benzoic anhydride is present and it reacts, in part, with aniline to form benzanilide and 1st acid, and is also hydrolysed to form 2nd acid. It is assumed that benzene sulphonanilide is formed from benzene sulphonyl chloride. Phenol is presumed to be formed from phenyl benzoate. The results are shown in Table 2.

(v) *Reaction of Benzoyl Peroxide with Sulphuryl Chloride in Benzene.*—Benzoyl peroxide (10·5 g), benzene (300 ml), and sulphuryl chloride (7·0 ml; 2·00 mol) were heated at 78 °C for 8 hr. Carbon dioxide (1·25, 1·10 mol) was evolved. Excess benzene and sulphuryl chloride were removed and chlorobenzene (0·82, 0·82 mol) was distilled. The residue, when worked up by the general procedure given by Lynch and Pausacker (1957*a*), gave the following: 1st benzoic acid (0·78, 0·76 mol), 2nd benzoic acid (0·20, 0·15 mol), phenol (0·11, 0·04 mol), diphenyl (0·10, 0·08 mol), and high-boiling residue (0·80, 0·56 g).

TABLE 2

REACTION OF BENZOYL PEROXIDE WITH THIONYL CHLORIDE AT 78 °C

$(PhCO_2)_2$ (g) ..	10·5	10·5	7
PhH (ml)	300	300	—
$SOCl_2$ (ml)	3·25 (1·00)	6·5 (2·00)	30
CO_2	0·82, 1·08	1·30, 1·36	Not determined
PhCl	0·68, 0·69	0·59, 0·57	0·57, 0·61
PhCOCl	0·0	0·20, 0·22	0·80, 0·70
$(PhCO)_2O$	0·39, 0·41	0·24, 0·27	0·08, 0·07
$PhCO_2Ph$	0·06, 0·05	0·13, 0·10	0·05, 0·09
$PhSO_2Cl$*	0·12, 0·07	0·12, 0·13	0·05, 0·04
Ph.Ph	0·07, 0·09	0·04, 0·06	0·0
High-boiling residue (g)	0·78, 0·68†	0·63, 0·65	0·44, 0·34

* Control experiments showed that there was approximately a 90% conversion of benzene sulphonyl chloride into benzene sulphonanilide.

† Found: C, 72·8; H, 6·9; Cl, 9·3; S, 7·8; O, 2·7%.

III. DISCUSSION

When either 1 or 2 mol of phosphorus trichloride react with benzoyl peroxide in benzene solution, benzoyl chloride and phenyl phosphonyl chloride are formed in good yields and a minor amount of diphenyl phosphonyl chloride can also be isolated. This would appear to be a convenient method of preparation of aromatic phosphonic acids as the phosphonyl chlorides can be quantitatively converted into the acid simply by standing in air. Other methods of preparing phosphonic acids have recently been reviewed by Freedman and Doak (1957). Aliphatic phosphonyl chlorides can be prepared from the hydrocarbon, phosphorus trichloride, and oxygen (Isbell and Wadsworth 1956).

$$RH + PCl_3 + \tfrac{1}{2}O_2 \rightarrow RPOCl_2 + HCl.$$

Benzene phosphonyl chloride is still formed when chlorobenzene is the solvent but *p*-chlorobenzene phosphonyl chloride is formed when *p*-chlorobenzoyl peroxide is heated with phosphorus trichloride in benzene. This shows that solvent does not enter into the reaction. When benzoyl peroxide reacts with benzene in the absence of phosphorus trichloride, diphenyl is one of the principal products (Lynch and Pausacker 1957*a*) and this is formed via the reaction of phenyl radicals with benzene. As diphenyl could not be isolated when phosphorus trichloride was present, it is suggested that phenyl radicals are not intermediates

in this reaction. Furthermore, chlorobenzene could not be isolated although its formation would be expected, if phenyl radicals were present, as shown in the following equation:

$$Ph\cdot + PCl_3 \rightarrow PhCl + \cdot PCl_2$$

(cf. Kharasch, Jensen, and Urry 1945). On the basis of these observations the following mechanism is proposed for the major reaction:

$$(PhCO_2)_2 \rightarrow 2PhCO_2\cdot, \quad \ldots\ldots (1)$$
$$PhCO_2\cdot + PCl_3 \rightarrow PhCO_2Cl + \cdot PCl_2, \quad \ldots\ldots (2)$$
$$\cdot PCl_2 + (PhCO_2)_2 \rightarrow Ph\cdot PCl_2 + CO_2 + PhCO_2\cdot, \quad \ldots\ldots (3)$$
$$PhPCl_2 + PhCO_2Cl \rightarrow PhPOCl_2 + PhCOCl. \quad \ldots\ldots (4)$$

The formation of diphenyl phosphonyl chloride may be written as follows:

$$PhPCl_2 + PhCO_2\cdot \rightarrow PhCO_2Cl + PhPCl\cdot, \quad \ldots\ldots (5)$$
$$PhPCl\cdot + (PhCO_2)_2 \rightarrow Ph_2PCl + CO_2 + PhCO_2\cdot, \quad \ldots\ldots (6)$$
$$Ph_2PCl + PhCO_2Cl \rightarrow Ph_2POCl + PhCOCl. \quad \ldots\ldots (7)$$

Although an ionic mechanism cannot be definitely eliminated, this radical chain mechanism is in accord with accepted mechanisms of allied reactions. Thus Kharasch, Jensen, and Urry (1945) have proposed that the $\cdot PCl_2$ radical is the chain carrier in the addition of phosphorus trichloride to 1-octene, using acetyl peroxide as initiator, and the PhPCl radical has similarly been proposed as an intermediate in addition of phenyldichlorophosphine to olefins (Walling 1957, p. 342). Finally, although benzoyl hypochlorite has never been isolated, Bockemuller and Hoffman (1935) have shown that benzoyl hypobromite is formed by the reaction of silver benzoate and bromine:

$$PhCO_2Ag + Br_2 \rightarrow PhCO_2Br + AgBr.$$

Its solution has a half-life of about 10 hr and is associated with a marked oxidizing power.

When benzoyl peroxide (1 mol) is heated with phosphorus trichloride alone, benzoyl chloride (2 mol) is the sole product of reaction. The reaction probably involves the initial formation of benzoic anhydride which then reacts with phosphorus trichloride to form benzoyl chloride:

$$(PhCO_2)_2 + PCl_3 \rightarrow (PhCO)_2O + POCl_3,$$
$$(PhCO)_2O + PCl_3 \rightarrow 2PhCOCl + POCl(?).$$

The first stage of this mechanism appears to be quite plausible as it is well known that tertiary phosphines react with benzoyl peroxide forming tertiary phosphine oxides and benzoic anhydride (Horner and Jurgeleit 1955; Denney and Greenbaum 1957). Independent experiments have shown that benzoic anhydride reacts with phosphorus trichloride, even in benzene solution, forming benzoyl chloride. Undoubtedly the above reaction does occur to a slight extent in benzene solution, as it has been found (see Table 1) that the yield of benzoyl

chloride is greater than that of phenyl phosphonyl chloride. Furthermore, it was found that appreciable amounts of *p*-chlorobenzoic anhydride, and relatively low yields of *p*-chlorobenzene phosphonyl chloride, could be isolated from the reaction of *p*-chlorobenzoyl peroxide with phosphorus trichloride in benzene solution. It has been suggested (Pausacker 1958) that electron-attracting substituents enhance the direct oxidizing power of substituted benzoyl peroxides and this may serve to explain the results observed with *p*-chlorobenzoyl peroxide. Although benzoyl peroxide could oxidize the phenyl dichlorophosphine, formed according to equation (**3**), to phenyl phosphonyl chloride, it is thought that benzoyl hypochlorite (eqn. (**2**)) should be more effective in this regard.

It is noted that phosphorus oxychloride does not enter into the reaction as the only products isolated from the reaction of phosphorus oxychloride, benzene, and benzoyl peroxide are those which are formed when the last two reagents are heated alone. Reynhart (1927) has found that phosphorus oxychloride alone is an indifferent solvent and merely facilitates the normal decomposition of benzoyl peroxide into phenyl benzoate, diphenyl, and carbon dioxide.

The reaction of benzoyl peroxide with sulphuryl chloride in benzene solution proceeds in an entirely different manner. The principal products are chlorobenzene, carbon dioxide, and benzoic acid (after hydrolysis). Thus, approximately 80 per cent. of the reaction occurs as follows:

$$(PhCO_2)_2 + SO_2Cl_2 \rightarrow PhCl + CO_2 + PhCO_2.SO_2Cl,$$
$$PhCO_2.SO_2Cl \xrightarrow[H_2O]{} PhCO_2H + H_2SO_4 + HCl.$$

Kharasch and Brown (1939), using a much higher ratio of sulphuryl chloride to both benzene and benzoyl peroxide, state that the principal reaction may be represented as

$$(PhCO_2)_2 + SO_2Cl_2 \rightarrow 2PhCl + 2CO_2 + SO_2.$$

The mechanism of the reaction may be represented as follows:

$$(PhCO_2)_2 \rightarrow 2PhCO_2\cdot, \quad \ldots\ldots\ldots\ldots\ldots\ldots (8)$$
$$PhCO_2\cdot \rightarrow Ph\cdot + CO_2, \quad \ldots\ldots\ldots\ldots\ldots\ldots (9)$$
$$Ph\cdot + SO_2Cl_2 \rightarrow PhCl + \cdot SO_2Cl, \quad \ldots\ldots\ldots\ldots (10)$$
$$\cdot SO_2Cl + (PhCO_2)_2 \rightarrow PhCO_2.SO_2Cl + Ph\cdot + CO_2. \quad \ldots\ldots (11)$$

Unlike the reaction involving phosphorus trichloride, phenyl radicals have been postulated as intermediates in this chain reaction. Confirmation of this is obtained from the fact that diphenyl can be isolated from the reaction mixture. The intermediate existence of $\cdot SO_2Cl$ radicals has previously been postulated in the chlorination of aliphatic hydrocarbons with sulphuryl chloride (see Walling 1957, p. 380). The normal reaction of benzoyl peroxide with benzene is assumed to account for about 20 per cent. of the total reaction.

The reaction of thionyl chloride with benzoyl peroxide in benzene solution gives a complex mixture of products, the nature of which indicates that all the

various types of reactions mentioned in the foregoing discussion are occurring simultaneously. These products may be accounted for as follows:

$$(PhCO_2)_2 + SOCl_2 \rightarrow PhCl + CO_2 + PhCO_2.SOCl, \quad \ldots\ldots\ldots\ldots (12)$$

$$(PhCO_2)_2 + SOCl_2 \rightarrow PhSOCl + PhCO_2Cl + CO_2, \quad \ldots\ldots\ldots\ldots (13)$$

$$PhSOCl + PhCO_2Cl \rightarrow PhSO_2Cl + PhCOCl, \quad \ldots\ldots\ldots\ldots\ldots (14)$$

$$(PhCO_2)_2 + SOCl_2 \rightarrow (PhCO)_2O + SO_2Cl_2, \quad \ldots\ldots\ldots\ldots\ldots (15)$$

$$(PhCO)_2O + SOCl_2 \rightarrow 2PhCOCl + SO_2, \quad \ldots\ldots\ldots\ldots\ldots\ldots (16)$$

$$(PhCO_2)_2 + PhH \rightarrow PhPh + PhCO_2Ph + PhCO_2H + CO_2, \text{ etc.}, \quad \ldots (17)$$

$$PhCO_2H + SOCl_2 \rightarrow PhCOCl + SO_2 + HCl. \quad \ldots\ldots\ldots\ldots\ldots (18)$$

Equation (**12**) is similar to the reaction postulated for sulphuryl chloride and equations (**13**), (**14**), and (**16**) resemble those, which have been postulated when phosphorus trichloride was involved. Independent experiments have shown that benzoic anhydride is only slowly converted to benzoyl chloride when heated with thionyl chloride in benzene. This accounts for the lower yield of benzoyl chloride, but higher yield of benzoic anhydride, when 1 mol, instead of 2 mol, of thionyl chloride was added (see Table 2). The yield of benzoic anhydride is still lower when thionyl chloride alone was used. The diphenyl is apparently formed according to equation (**17**) and not by thermal decomposition. That is,

$$(PhCO_2)_2 \rightarrow PhPh + 2CO_2,$$

as it could not be isolated when benzene was absent. On the other hand, phenyl benzoate is produced in small yield when thionyl chloride alone was used. It is presumably formed by direct thermal decomposition. That is,

$$(PhCO_2)_2 \rightarrow PhCO_2Ph + CO_2.$$

In all these reactions the mechanisms proposed are tentative as they could proceed via an intermediate complex which then breaks down to give the products. Formation of such complexes has been postulated for the reaction of benzoyl peroxide with sulphides (Horner and Jurgens 1957), tertiary amines (Horner 1955; Imoto and Takemoto 1956), and tertiary phosphines (Horner and Jurgeleit 1955; Denney and Greenbaum 1957). In the first case an electron transfer reaction, which does not distinguish between ionic and radical mechanisms, is preferred and in the last two cases ionic mechanisms are favoured.

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AMINO ACIDS AND PEPTIDES*

IV. INTERMEDIATES FOR THE SYNTHESIS OF CERTAIN CYSTINE-CONTAINING PEPTIDE SEQUENCES IN INSULIN†

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[*Manuscript received January* 20, 1958]

Summary

The synthesis is described of various derivatives of the peptides L-glutaminyl-*S*-benzyl-L-cysteine, L-glutaminyl-*S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteine, *S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteine, *S*-benzyl-L-cysteinyl-L-alanine, *S*-benzyl-L-cysteinyl-L-alanyl-L-serine, L-alanyl-L-serine, L-valyl-*S*-benzyl-L-cysteine, L-alanyl-L-seryl-L-valyl-*S*-benzyl-L-cysteine, *S*-benzyl-L-cysteinyl-L-alanyl-L-seryl-L-valyl-*S*-benzyl-L-cysteine, *S*-benzyl-L-cysteinylglycine, and L-leucyl-*S*-benzyl-L-cysteinylglycine.

I. INTRODUCTION

The work described in this and the following papers forms part of a programme for the synthesis of cystine derivatives and peptides and for the study of their properties in relation to the chemistry of wool (Swan 1955*a*). It has been shown that the disulphide bonds in wool and other proteins can be divided into fractions of different reactivity (for reviews, see Phillips 1946; Alexander and Hudson 1954). Wide variations in disulphide bond reactivity can also be found in quite simple cystine derivatives (Schöberl and Krumey 1938; Cecil and McPhee 1955; McPhee 1956) and in insulin (Lindley 1955; Cecil and Loening 1957). We hope to throw more light on this problem by studying cystine-containing fragments of the insulin molecule and comparing these with insulin on the one hand and with smaller disulphides such as cystine on the other.

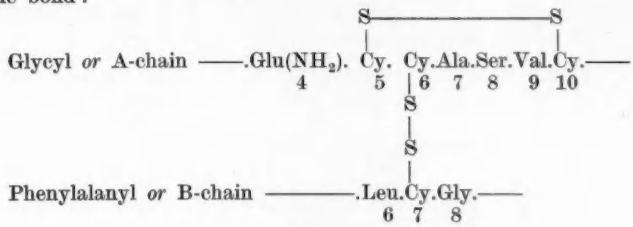
The portion of the beef-insulin molecule (Sanger and Tuppy 1951; Sanger and Thompson 1953; Ryle *et al.* 1955; Sanger, Thompson, and Kitai 1955),

* The following papers constitute Parts I to III of this series: I. The synthesis and lanthionine-forming properties of some derivatives of cystine. J. M. Swan (1955).—*Proc. Int. Wool Text. Res. Conf. Aust.* **C**: 25; II. Preparation of the tetraethyl pyrophosphite reagent. J. A. Maclaren (1955).—*Proc. Int. Wool Text. Res. Conf. Aust.* **C**: 168; III. The synthesis of L-glutaminylglycine and L-*iso*glutaminylglycine. J. M. Swan (1955).—*Proc. Int. Wool Text. Res. Conf. Aust.* **C**: 175.

† A preliminary report of some aspects of this work has been published in *Proc. Int. Wool Text. Res. Conf. Aust.* **C**: 164.

‡ Biochemistry Unit, Wool Textile Research Laboratories, C.S.I.R.O., Melbourne.

in which we are presently interested contains both an inter- and an intrachain disulphide bond :*



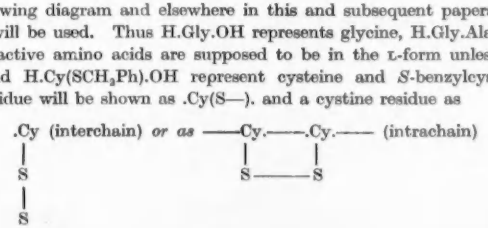
Reduction of the disulphide bonds in this unit would give the two fragments leucylcysteinylglycine and glutaminylcysteinylcysteinylalanylserylvalylcysteine. It should be possible to obtain these peptides by debenzylation of the corresponding *S*-benzylcysteine- or *N*-protected-*S*-benzylcysteine compounds, using sodium in liquid ammonia. This method has now been widely exploited, for example, in the synthesis of glutathione (du Vigneaud and Miller 1936), oxytocin (du Vigneaud *et al.* 1954 ; Boissonnas *et al.* 1955 ; Rudinger, Honzl, and Zaoral 1956*a*), oxytocin analogues (Boissonnas *et al.* 1956 ; Rudinger, Honzl, and Zaoral 1956*b* ; Katsoyannis 1957), lysine vasopressin (Bartlett *et al.* 1956), arginine vasopressin (du Vigneaud, Gish, and Katsoyannis 1954), and various peptides containing cysteine and glycine (Heaton, Rydon, and Schofield 1956).

In the present paper, the synthesis of the tripeptide L-leucyl-*S*-benzyl-L-cysteinylglycine and of various intermediates required for the preparation of the heptapeptide L-glutaminyl-*S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteinyl-L-alanyl-L-seryl-L-valyl-*S*-benzyl-L-cysteine is described. The synthesis of the latter compound and of the corresponding heptapeptide having a glycyl residue in place of the seryl residue (sheep insulin) will be reported in a subsequent paper.

II. Results and Discussion

The peptide linkages effected, together with methods used, are presented in Table 1. Of particular interest is the preparation of the tripeptide derivative *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-alanyl-L-serine methyl ester both from *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine and L-alanyl-L-serine methyl ester by the mixed anhydride method and also from *S*-benzyl-*N*-benzyloxy-

* In the following diagram and elsewhere in this and subsequent papers the abbreviations of Brand (1946) will be used. Thus H.Gly.OH represents glycine, H.Gly.Ala.OH glycylalanine, and all optically-active amino acids are supposed to be in the L-form unless otherwise stated. H.Cy(SH).OH and H.Cy(SCH$_2$Ph).OH represent cysteine and *S*-benzylcysteine respectively. A half-cystine residue will be shown as .Cy(S—). and a cystine residue as



carbonyl-L-cysteinyl-L-alanine azide and serine methyl ester. In neither of these two syntheses was it found necessary to protect the serine hydroxy group. For the addition of single amino acid residues we have found the new phosphorus oxychloride method of Wieland and Heinke (1956) to give in general very good

TABLE 1

PEPTIDE SEQUENCES EFFECTED

Sequence	Protecting Groups†		Method‡	Yield (%)
	Amino	Carboxyl		
.Glu(NH_2)*.Cy(SCH_2)Ph.	Tosyl	Mg salt	Pyroglutamyl chloride	20 (overall)
	Tosyl	Et	Pyroglutamyl chloride	76 (overall)
	Z	$PhCH_2$	$POCl_3$	33
	Z	Et	$POCl_3$	35
	Z	Et	$ClCO_2Et$	<35
.Glu(NH_2)*.Cy(SCH_2Ph).Cy(SCH_2Ph)	Z	Et	$POCl_3$	94
	Tosyl	$PhCH_2$	Pyrophosphite	low
.Cy(SCH_2Ph)*.Cy(SCH_2Ph).	Z	Et	$ClCO_2Et$	67
	Z	Et	$POCl_3$	52
	Z	Me	$ClCO_2Et$	low
	Z	Me	Azide	low
	Formyl	Me	$ClCO_2Et$	low
.Cy(SCH_2Ph)*.Ala	Z	Me	$ClCO_2Et$	80
	Z	Et	$ClCO_2Et$	—
.Ala*.Ser.	Z	Me	$ClCO_2Et$	51
.Cy(SCH_2Ph)*.Ala.Ser	Z	Me	$ClCO_2Et$	—
.Cy(SCH_2Ph).A'a*.Ser	Z	Me	Azide	73
.Val*.Cy(SCH_2Ph).	Z	$PhCH_2$	$ClCO_2Et$	76
.Ala.Ser*.Val.Cy(SCH_2Ph)	Z	$PhCH_2$	Azide	74
.Cy(SCH_2Ph).Ala.Ser*.Val.Cy(SCH_2Ph)	Z	$PhCH_2$	Azide	—
.Cy(SCH_2Ph)*.Gly	Z	Et	Azide	low
	Z	Et	$ClCO_2Et$	72
	Z	$PhCH_2$	$ClCO_2Et$	77
.Leu*.Cy(SCH_2Ph).Gly	Z	$PhCH_2$	$ClCO_2Et$	50

* Denotes new bond formed.

† Tosyl represents toluene-*p*-sulphonyl, Z represents benzyloxycarbonyl (" carbobenzoxy "), Me, Et, and $PhCH_2$ denote methyl, ethyl, and benzyl esters respectively.

‡ The methods of peptide synthesis have been reviewed by Fruton (1949), Shapiro (1952), Wieland (1951, 1954, 1957), du Vigneaud (1955), Kenner (1955, 1956), and Springall and Law (1956).

yields. We have not yet employed it for linking di- and higher peptides since the possibility of partial racemization in such cases has not yet been investigated, and we have preferred to use for these the well-established azide method.

The following free peptides and peptide esters have been obtained in the course of this work: L-glutaminyl-*S*-benzyl-L-cysteine, *S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteine ethyl ester, L-alanyl-L-serine methyl ester,

L-valyl-*S*-benzyl-L-cysteine benzyl ester, L-valyl-*S*-benzyl-L-cysteine, *S*-benzyl-L-cysteinylglycine, and L-leucyl-*S*-benzyl-L-cysteinylglycine. In all cases the *N*-protecting-benzyloxycarbonyl group was removed with anhydrous HBr in acetic acid; the carboxyl-protecting benzyl ester can be removed simultaneously or else retained according to the severity of treatment (Ben-Ishai and Berger 1952; Ben-Ishai 1954). Using 6N HBr in acetic acid at room temperature, we find that removal of the benzyloxycarbonyl group is generally complete in about 30 min; if the peptide benzyl ester is required and the hydrobromide fails to crystallize, it must be precipitated by addition of ether. Debenzylation of benzyl esters with anhydrous HBr is much superior to alkaline saponification of methyl or ethyl peptide esters, especially when *S*-benzylcysteine residues are present, which under alkaline conditions can very easily lose toluene-ω-thiol (see below). For this reason *S*-benzyl-L-cysteine benzyl ester becomes an important intermediate, and its preparation in high yield from *S*-benzyl-L-cysteine under conditions not leading to racemization is described in Section III.

In converting *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine hydrazide or *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-alanine hydrazide to the corresponding azide with cold nitrous acid, a large proportion of the corresponding amide was formed if the experimental conditions were not rigorously controlled. Hegedüs (1948), Roberts (1954), and Roeske *et al.* (1956) have also reported amide formation with *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine azide; other examples of this interesting decomposition of azide to amide are given by Weerman (1918), Prelog and Wieland (1946), Olsen and Erkemeyer (1948), and Cook and Elvidge (1949).

Possibly due to steric factors, some peptide esters containing the *S*-benzylcysteine residue were converted to the hydrazide only with difficulty. Earlier, methanol or ethanol was used as solvent, and raising the reaction temperature to reflux usually resulted in the formation of toluene-ω-thiol as evidenced by the odour; from *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinylglycine ethyl ester a comparatively large quantity of dibenzyl disulphide was isolated. Success was achieved in most instances by keeping the temperature at 37–50 °C for several hours or days. Even these conditions proved too vigorous for the successful preparation of *S*-benzyl-*N*-toluene-*p*-sulphonyl-L-cysteine hydrazide from the methyl ester; the product was found to be more than 10 per cent. racemized. Apparently toluene-ω-thiol is formed by a base-catalysed β-elimination,

$$\begin{array}{l} \mathrm{RNHCHCOR'} \\ \quad\quad | \\ \mathrm{CH_2SCH_2Ph} \end{array} \rightleftarrows \begin{array}{l} \mathrm{RNHCCOR'} \\ \quad\quad \| \\ \mathrm{CH_2} \end{array} + \mathrm{PhCH_2SH}$$

and the thiol can then either recombine with the aminoacrylic acid derivative to give either the D- or L-adduct or else may be slowly oxidized by air to dibenzyl disulphide. Latterly, we have effected an improvement in the formation of hydrazides from refractory esters by conducting the reaction at 40 °C in *n*-butanol. The special virtues of this solvent in accelerating hydrazide formation were demonstrated for various simple esters by Ferren, Miller, and Day (1957).

Compounds containing both a glutamine and an *S*-benzylcysteine residue are an especially difficult problem, since vigorous or prolonged reaction with hydrazine can bring about the undesired conversion of the side-chain $-CONH_2$ group to $-CONHNH_2$. For example, on keeping toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine ethyl ester in ethanolic hydrazine for 118 hr at 40 °C, much unchanged starting material was recovered, m.p. 170 °C, together with a product, m.p. 180 °C, which gave analytical figures for, but a m.p. depression with, the starting material, and is presumably a diastereoisomer formed by racemization at the *S*-benzylcysteine residue. On the other hand, reaction with hydrazine in *n*-butanol at 40 °C for 18 hr gives toluene-*p*-sulphonyl-L-glutamyl-γ-hydrazide-α-*S*-benzyl-L-cysteine hydrazide, m.p. 179 °C, also prepared from toluene-*p*-sulphonyl-L-pyroglutamyl-*S*-benzyl-L-cysteine ethyl ester* by reaction with hydrazine. The desired toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine hydrazide has not yet been obtained. However, it has been found possible to convert benzyloxycarbonyl-L-glutaminyl-*S*-benzyl-L-cysteine ethyl ester to the corresponding monohydrazide in 82 per cent. yield using hydrazine in *n*-butanol; this is a noteworthy difference between toluene-*p*-sulphonyl and benzyloxycarbonyl as *N*-protecting groups.

Benzyloxycarbonyl-L-glutaminyl-*S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteine ethyl ester was obtained in very high yield from benzyloxycarbonyl-L-glutamine and *S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteine ethyl ester, and conversion to the hydrazide again proceeded smoothly in warm butanol in over 80 per cent. yield. This tripeptide hydrazide is the intermediate of choice for preparation of the desired heptapeptide to be described later.

In effecting the glutaminyl-*S*-benzylcysteine sequence by the toluene-*p*-sulphonyl-L-pyroglutamyl chloride method (Swan and du Vigneaud 1954; Swan 1955*b*; Stedman 1957) some difficulty was encountered in opening the pyroglutamyl (5-oxopyrrolidine) ring with ammonia while avoiding side reactions. Thus toluene-*p*-sulphonyl-L-pyroglutamyl-*S*-benzyl-L-cysteine ethyl ester was unchanged after refluxing in a mixture of chloroform and aqueous ammonia but gave the desired glutamine peptide ester in 90 per cent. yield on reaction with aqueous ammonia in warm ethanol. Using dioxan as solvent the product was contaminated with some toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine amide. The corresponding pyroglutamyl methyl ester was recovered more or less unchanged from various attempts to convert it to the glutamine derivative, especially using solvents such as chloroform, dioxan, or dimethylformamide. On the other hand, reaction with aqueous ammonia in hot ethanol gave toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine amide in 60 per cent. yield. It does appear therefore that ethanol favours reaction of ammonia with the pyroglutamyl ring, but simultaneous conversion of ester groups to amide may then become troublesome.

* Pyroglutamic acid is used in *Chemical Abstracts* to denote pyrrolid-5-one-2-carboxylic acid (5-oxo-2-pyrrolidinecarboxylic acid), and this term is especially convenient when naming peptides containing this heterocycle.

III. Experimental

Melting points are uncorrected. Analyses are by the C.S.I.R.O. Microanalytical Laboratory.

(a) *Amino Acids and Amino Acid Esters*

L-Leucine, L-glutamic acid, and L-cystine were obtained commercially. L-Serine was prepared from silk fibroin by the method of Stein and Moore (1949) and had $[\alpha]_D^{20}$ +12·5° (*c*, 0·90 in 6N HCl). L-Alanine was prepared by (i) the latter method, having $[\alpha]_D^{20}$ +14·1° (*c*, 1·01 in 6N HCl); (ii) asymmetric enzymatic synthesis from DL-alanine by the method of Doherty and Popenoe (1951), having $[\alpha]_D^{20}$ +12·2° (*c*, 0·99 in 6N HCl). *S*-Benzyl-L-cysteine was prepared from L-cystine by the method of Wood and du Vigneaud (1939), and had m.p. 217–219 °C, $[\alpha]_D^{20}$ +25·5° (*c*, 1·02 in 1N NaOH), after recrystallization from a large volume of water. L-Glutamine was prepared by the method of Swan and du Vigneaud (1954) and glutamic acid γ-ethyl ester by the method of Miller and Waelsch (1952).

L-Valine was obtained commercially and was also prepared by resolution of caproyl-DL-valine, using the papain/aniline method (Doherty and Popenoe 1951). The caproyl-L-valine anilide, m.p. 182–183 °C, $[\alpha]_D^{20}$ −58·4° (*c*, 1·8 in acetic acid) was hydrolysed by boiling with 20% HCl (12 ml/g) for 4 hr, and the amino acid, $[\alpha]_D^{20}$ +29·2° (*c*, 3·08 in water), was isolated using "Zeokarb IR4–B" resin. Initially, benzoyl-L-valine anilide, m.p. 214–215 °C, $[\alpha]_D^{19}$ −82° (*c*, 5 in $CHCl_3$) (cf. Fox *et al.* 1950), was prepared by the papain synthesis, but various attempts to hydrolyse this led to partial racemization (up to 40%) of the L-valine. The formation of partially racemized lysine on acid hydrolysis of dibenzoyl-L-lysine anilide has been reported by Murachi (1956).

Glycine Benzyl Ester Toluene-p-*sulphonate*.—This was prepared by the method of Miller and Waelsch (1952) and crystallized from chloroform/light petroleum (b.p. 60–90 °C) as colourless plates, m.p. 133–135 °C (Found: C, 57·1; H, 5·9; N, 4·1%. Calc. for $C_{16}H_{19}O_5NS$: C, 57·0; H, 5·9; N, 4·2%).

L-Serine methyl ester hydrochloride was prepared by the method of Harris and Fruton (1951). *L-Alanine methyl ester hydrochloride* was prepared similarly in 90% yield. It crystallized in slightly hygroscopic needles, m.p. 154–155 °C, from chloroform/light petroleum (b.p. 40–60 °C) (Found: N, 9·9; OMe, 21·6%. Calc. for $C_4H_{10}O_2NCl$: N, 10·0; OMe, 22·2%). L-Alanine ethyl ester was prepared from silk fibroin by the method of Fischer and Skita (1901). Two distillations using a small column gave a fraction, b.p. 68 °C/42 mm, n_D^{20} 1·4228.

S-Benzyl-L-cysteine ethyl ester hydrochloride was prepared from *S*-benzyl-L-cysteine by Hooper's (1953) modification of the method of Harington and Pitt Rivers (1944). Hooper has shown that unless the alcoholic HCl solution is refluxed briefly, the product contains some unchanged *S*-benzylcysteine. Yield 89%, m.p. 159–160 °C. Harington and Pitt Rivers (1944) report m.p. 156–157 °C, Hooper (1953) obtained m.p. 155 °C. *S-Benzyl-L-cysteine methyl ester hydrochloride* was prepared by refluxing *S*-benzyl-L-cysteine (16 g) in methanol (150 ml) saturated with dry HCl. After concentrating to 75 ml the product (11·4 g) was precipitated by the addition of ether, m.p. 151–152 °C, after recrystallization from methanol/ether/light petroleum (Found: N, 5·1; S, 12·5%. Calc. for $C_{11}H_{16}O_2NSCl$: N, 5·3; S, 12·2%).

S-*Benzyl*-L-*cysteine Benzyl Ester*.—The best method for preparing this compound was found to be as follows (cf. Cipera and Nicholls 1955): *S*-Benzyl-L-cysteine (21·1 g; 0·1 mole), toluene-*p*-sulphonic acid monohydrate (20·9 g; 0·11 mole), and benzyl alcohol (40 ml) were mixed in a 500 ml round-bottomed flask fitted with a Soxhlet containing a mixture of anhydrous Na_2SO_4 and $MgSO_4$ supported on a small pad of cotton wool, and surmounted by a reflux condenser. The reaction mixture was warmed on the water-bath until solution was attained (5 min), then carbon tetrachloride (150 ml) was added gradually. After heating under reflux for 6 hr the removal of water by the carbon tetrachloride appeared to be complete and the product commenced to crystallize. Additional carbon tetrachloride (100 ml) was added, and after keeping overnight the S-*benzyl*-L-*cysteine benzyl ester toluene*-p-*sulphonate* was collected and washed with

carbon tetrachloride. Yield, 41·0 g (87%), m.p., 156–158 °C, raised to 159–160 °C on recrystallization from 90% acetone, ethanol, or ethanol/ether; $[\alpha]_D^{20}$ —20·4° (*c*, 1·32 in 90% EtOH) (Found: C, 60·7; H, 5·5; N, 2·9%. Calc. for $C_{24}H_{27}O_5NS_2$: C, 60·9; H, 5·8; N, 3·0%). Hooper *et al.* (1956), who have prepared this compound independently by a similar method (azeotropic distillation using benzene), report m.p. 159 °C.

The salt was converted to the free ester (an oil, quantitative yield) by dissolving in 20% Na_2CO_3 and extracting twice with ether. The triethylamine/chloroform method (Miller and Waelsch 1952) for obtaining the free base gave only 20% conversion, and it was found that addition of ether to the chloroform/triethylamine solution caused mainly reprecipitation of the sparingly soluble *S*-benzyl-L-cysteine benzyl ester toluene-*p*-sulphonate. This salt could even be crystallized unchanged from 2N HCl. The triethylamine method was successful, however, with the benzene sulphonate (see below). The free ester with dry HCl in ether yielded a crystalline *hydrochloride*, m.p. 129–130 °C, from acetone/ether, $[\alpha]_D^{21·5}$ —18·9° (*c*, 1·21 in EtOH) (Found: C, 60·3; H, 6·1; N, 4·2%. Calc. for $C_{17}H_{20}O_2NSCl$: C, 60·4; H, 6·0; N, 4·2%). Hooper *et al.* (1956) report m.p. 134 °C.

S-Benzyl-L-cysteine benzyl ester was also prepared as its *benzenesulphonate* by the general method of Miller and Waelsch (1952). After evaporation of the benzyl alcohol the product was crystallized from acetone/ether or methanol/ether, m.p. 134–135 °C, yield 70–90%, $[\alpha]_D^{21·5}$ —17·2° (*c*, 2·0 in EtOH) (Found: C, 59·8; H, 5·7; N, 3·1%. Calc. for $C_{23}H_{25}O_5NS_2$: C, 60·1; H, 5·5; N, 3·1%). The free ester was obtained by dissolving this salt with 1 equivalent of triethylamine in chloroform and precipitating triethylamine benzenesulphonate by the addition of ether. Using toluene-*p*-sulphonic acid monohydrate in place of benzenesulphonic acid in this preparation gave on a number of occasions products melting between 154 and 157 °C, which were shown to be partly racemized. After conversion to the hydrochloride, fractional crystallization gave small yields of *S-benzyl-DL-cysteine benzyl ester hydrochloride*, m.p. 154–154·5 °C (Found: C, 60·1; H, 5·9; O, 9·9; Cl, 10·2%. Calc. for $C_{17}H_{20}O_2NSCl$: C, 60·4; H, 6·0; O, 9·5; Cl, 10·5%). This material was converted to the free base and then to *S-benzyl-DL-cysteine benzyl ester toluene-p-sulphonate*, m.p. 145–148 °C (Found: C, 61·2; H, 5·8; N, 2·6%. Calc. for $C_{24}H_{27}O_5NS_2$: C, 60·9; H, 5·8; N, 3·0%). Neither of these salts showed any optical rotation. In other preparations using toluene-*p*-sulphonic acid and allowing the temperature to exceed 120 °C, the product was almost wholly racemic.

Leach and Lindley (1954) have reported the preparation of *S*-benzyl-L-cysteine benzyl ester by Miller and Waelsch's (1952) method. They record m.p. 148–151 °C for the hydrochloride, which is close to that of our *racemic* hydrochloride, m.p. 154–154·5 °C. Leach and Lindley used toluene-*p*-sulphonic acid monohydrate rather than benzenesulphonic acid (Lindley, personal communication) and a sample of their *S*-benzylcysteine benzyl ester toluene-*p*-sulphonate, m.p. 147–150 °C (kindly provided by Dr. Lindley), has now been shown to be racemic, having $[\alpha]_D^{20}$ 0° (*c*, 1·40 in EtOH).

(*b*) *N-Protected Amino Acids*

The benzyloxycarbonyl derivatives were prepared by the general method of Bergmann and Zervas (1932). Benzyloxycarbonyl-L-alanine (yield 77%) was obtained as plates, m.p. 85–86 °C, Bergmann and Zervas (1932) record m.p. 84 °C; benzyloxycarbonyl-L-valine and -L-leucine were obtained as non-crystalline glasses (cf. Synge 1948); *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine, m.p. 94–96 °C, was obtained in 85% yield; Harington and Mead (1936) record m.p. 93–95 °C.

Reaction of benzylchlorocarbonate with L-glutamic acid γ-ethyl ester (Hanby, Waley, and Watson 1950), followed by treatment with aqueous ammonia (Miller and Waelsch 1952), gave benzyloxycarbonyl-L-glutamine, m.p. 136–137·5 °C, showing no m.p. depression with a sample prepared directly from synthetic L-glutamine. Toluene-*p*-sulphonyl-L-glutamic acid was prepared according to Swan and du Vigneaud (1954), and toluene-*p*-sulphonyl-L-glutamyl dichloride, m.p. 75–78 °C, and toluene-*p*-sulphonyl-L-pyroglutamyl chloride, m.p. 106–107 °C, following the directions of Stedman (1957).

(i) *S-Benzyl-N-formyl-L-cysteine.*—Acetic anhydride (2 ml) was added to 98% formic acid (10 ml), the mixture was kept for 10 min, cooled to room temperature, and added to a solution

of *S*-benzyl-L-cysteine (2·1 g) in 98% formic acid (20 ml). The mixture was kept for 2 hr then diluted with water and kept at 0 °C giving *S-benzyl-N-formyl-L-cysteine*, m.p. 126 °C, after crystallization from water and then ethyl acetate/light petroleum (b.p. 40–60 °C). Yield 1·5 g, $[\alpha]_D^{18}$ —8·6° (*c*, 5·0 in EtOH) (Found: N, 5·6; S, 13·7%. Calc. for $C_{11}H_{13}O_3NS$: N, 5·8; S, 13·4%).

(ii) *S-Benzyl-N-toluene-p-sulphonyl-L-cysteine and Derivatives.*—*S*-Benzyl-L-cysteine (10·5 g; 0·05 mole) was dissolved in N NaOH (50 ml) at 15 °C. Finely powdered toluene-*p*-sulphonyl chloride (12·5 g) was added and the mixture stirred vigorously at 12–15 °C for 45 min, during which time N NaOH (50 ml) was added in portions to keep the pH *c.* 9. The excess chloride was filtered and the filtrate acidified to congo red with 5N HCl, giving 14·0 g (77%) of product which crystallized from benzene in needles, m.p. 124–124·5 °C, $[\alpha]_D^{20}$ +13·3° (*c*, 4·5 in 2-butanone). Honzl and Rudinger (1955) record m.p. 125–126 °C. The acid (3·65 g) was refluxed for 3 hr in methanol (50 ml) containing H_2SO_4 (1 ml); the mixture was then concentrated to 20 ml and water added, giving an excellent yield of *product* which was washed in turn with water, $NaHCO_3$ and water, and then recrystallized from aqueous methanol.

(iii) *S-Benzyl-N-toluene-p-sulphonyl-L-cysteine methyl ester* had m.p. 73–73·5 °C, $[\alpha]_D^{18}$ +21·4° (*c*, 5·0 in MeOH) (Found: C, 57·1; H, 5·7; S, 16·8%. Calc. for $C_{18}H_{21}O_4NS_2$: C, 57·0; H, 5·6; S, 16·9%). The above methyl ester (1 g) was kept in ethanol (20 ml) with 80% hydrazine hydrate (2 ml) for 3 days at 35 °C. On scratching the walls of the vessel and keeping 30 min, *S-benzyl-N-toluene-p-sulphonyl-DL-cysteine hydrazide* crystallized (0·1 g) and was recrystallized in small needles from ethanol, m.p. 162 °C (Found: C, 54·1; H, 5·6; N, 17·0%. Calc. for $C_{17}H_{21}O_3N_3S_2$: C, 53·8; H, 5·6; N, 16·9%); $[\alpha]_D^{19}$ 0·0° (*c*, 0·66 in glacial acetic acid). Dilution of the filtrate with an equal volume of water gave *S-benzyl-N-toluene-p-sulphonyl-L-cysteine hydrazide*, 0·6 g, m.p. 127·5 °C, lustrous plates from ethanol (Found: C, 54·1; H, 5·6; N, 17·2%), $[\alpha]_D^{19}$ —9·3° (*c*, 0·64 in glacial acetic acid). This hydrazide was recovered unchanged on keeping in alcoholic triethylamine for 3 days at 35 °C, but was readily racemized on heating for a short time at 155 °C.

(c) *Compounds related to the Sequence —Glu(NH₂).Cy(SCH₂Ph).Cy(SCH₂Ph)—*

(i) *Toluene-p-sulphonyl-L-pyroglutamyl-S-benzyl-L-cysteine.*—*S*-Benzyl-L-cysteine (3·85 g) was dissolved in boiling water (100 ml) containing magnesium oxide (2 g) and the mixture was cooled rapidly in a glass bottle to give a thick paste. Toluene-*p*-sulphonyl-L-pyroglutamyl chloride (5·0 g) was added, together with some glass beads, and the mixture was shaken vigorously with frequent additions of 0·5 ml portions of dimethylformamide, until further additions no longer caused the reaction to continue exothermically. After a total of 4 hr the solution was acidified, the gummy precipitate washed by decantation, dissolved in $NaHCO_3$, reprecipitated, and finally crystallized from aqueous methanol, yielding 2·6 g (30%) of *product*, m.p. 89–90 °C (Found: C, 54·9; H, 5·2; S, 13·5%. Calc. for $C_{22}H_{24}O_6N_2S_2$: C, 55·4; H, 5·1; S, 13·5%).

(ii) *Toluene-p-sulphonyl-L-glutaminyl-S-benzyl-L-cysteine.*—Conversion to the glutaminyl compound was best effected by dissolving the above product (either crude or recrystallized) in warm 30% NH_4OH (7 ml/g) and heating for 2 hr on a steam-bath. Toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine separated on acidification in 67% yield, m.p. 170–174 °C, raised to 183 °C on crystallization from ethanol, $[\alpha]_D^{21}$ +13·6° (*c*, 2·0 in 0·5N $KHCO_3$) (Found: C, 53·4; H, 5·4; O, 19·7; N, 8·5%. Calc. for $C_{22}H_{27}O_6N_3S_2$: C, 53·5; H, 5·5; O, 19·5; N, 8·5%).

(iii) *Toluene-p-sulphonyl-L-pyroglutamyl-S-benzyl-L-cysteine Ethyl Ester.*—*S*-Benzyl-L-cysteine ethyl ester hydrochloride (2·1 g) was dissolved in chloroform (15 ml) containing triethylamine (2 equiv.; 2·1 ml). The solution was cooled in an ice-bath and toluene-*p*-sulphonyl-L-pyroglutamyl chloride (2·3 g) was added. After 5 min the almost clear solution was evaporated, the residue treated with water, and the solid *product* filtered. Yield, 3·2 g (84%), m.p. 142–145 °C, raised to 150 °C on crystallization from ethanol, $[\alpha]_D^{21·5}$ —17·0° (*c*, 1·8 in dioxan) (Found: C, 57·3; H, 5·7; O, 19·3; S, 12·9%. Calc. for $C_{24}H_{28}O_6N_2S_2$: C, 57·1; H, 5·6; O, 19·0; S, 12·7%). When this preparation was repeated using toluene-*p*-sulphonyl-L-glutamyl dichloride in place of toluene-*p*-sulphonyl-L-pyroglutamyl chloride, the same product was obtained in 65%

yield (Found: C, 57·0; H, 5·7; O, 19·2%). Toluene-*p*-sulphonyl-L-pyroglutamyl-*S*-benzyl-L-cysteine ethyl ester was characterized by allowing it to react with cold aqueous ethanolic hydrazine. After 2 hr, a crystalline product separated in high yield, m.p. 144–145 °C, from ethanol, and analysed for *toluene*-p-*sulphonyl*-L-*glutamyl*-γ-*hydrazide*-α-S-*benzyl*-L-*cysteine ethyl ester* (Found: O, 17·0; S, 12·0%. Calc. for $C_{24}H_{32}O_6N_6S_2$: O, 17·1; S, 12·3%). From the filtrate there separated a trace of a second product, m.p. 177–179 °C, after crystallization from ethanol, analysing for toluene-*p*-sulphonyl-L-glutamyl-γ-hydrazide-α-*S*-benzyl-L-cysteine hydrazide (Found: O, 15·3; N, 15·9%. Calc. for $C_{22}H_{30}O_5N_6S_2$: O, 15·3; N, 16·1%).

(iv) *Toluene*-p-*sulphonyl*-L-*glutaminyl*-S-*benzyl*-L-*cysteine Ethyl Ester*. — (1) Toluene-*p*-sulphonyl-L-pyroglutamyl-*S*-benzyl-L-cysteine ethyl ester (1 g) was dissolved in hot ethanol (10 ml) and 30% NH_4OH (10 ml) added. After standing for 1 hr, the solution was evaporated and the product crystallized from ethanol. Yield 90–95%, m.p. 178–180 °C, with some sintering above 170 °C, $[\alpha]_D^{21·5}$ +26·1° (*c*, 1·0 in dioxan) (Found: C, 55·5; H, 6·0; O, 17·9; N, 7·5%. Calc. for $C_{24}H_{31}O_6N_3S_2$: C, 55·3; H, 6·0; O, 18·4; N, 8·1%).

(2) Toluene-*p*-sulphonyl-L-pyroglutamyl-*S*-benzyl-L-cysteine ethyl ester (6 g) was dissolved in purified dioxan (30 ml) and 30% NH_4OH (15 ml) added. After standing for 18–24 hr at room temperature, the solution was evaporated and the residue digested with hot chloroform (100 ml). After cooling, a solid product (0·9 g, m.p. 205–210 °C) was isolated, which after recrystallization from 95% ethanol gave analytical figures for *toluene*-p-*sulphonyl*-L-*glutaminyl*-S-*benzyl*-L-*cysteine amide*, m.p. 226 °C (Found: C, 53·7; H, 5·6; N, 11·2%. Calc. for $C_{22}H_{28}O_5N_4S_2$: C, 53·6; H, 5·7; N, 11·4%). The chloroform filtrate was evaporated to low bulk and diluted with several volumes of ether, giving toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine ethyl ester, identical with the material described above. Yield 4·5 g (73%) (Found: C, 55·2; H, 5·9; N, 8·3%). The pyroglutamyl ethyl ester was recovered unchanged after refluxing 5 hr with 2 vol of chloroform and 1 vol of 30% NH_4OH.

(v) *Toluene*-p-*sulphonyl*-L-*pyroglutamyl*-S-*benzyl*-L-*cysteine Methyl Ester*. — Toluene-*p*-sulphonyl-L-pyroglutamyl chloride (11·6 g) was added in one portion with cooling to a solution of *S*-benzyl-L-cysteine methyl ester (10·1 g) in chloroform (30 ml) containing triethylamine (10·6 ml). After keeping overnight at room temperature the chloroform solution was washed with dilute HCl, $NaHCO_3$, and water, the solvent evaporated and the residue crystallized from methanol, giving 15 g of *product*, m.p. 149 °C, raised to 150 °C on recrystallization, $[\alpha]_D^{23}$ +11·6° (*c*, 2·8 in dioxan) (Found: C, 56·6; H, 5·4; O, 19·3; N, 5·2%. Calc. for $C_{23}H_{26}O_6N_2S_2$: C, 56·3; H, 5·3; O, 19·6; N, 5·7%). Various attempts to convert this compound to toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine methyl ester were unsuccessful. It was recovered more or less unchanged after shaking a chloroform solution with 30% NH_4OH for 4 hr, after keeping for 4 hr in liquid ammonia, after standing for 3 days in aqueous methanolic ammonia, or after refluxing 1 hr in either dioxan or dimethylformamide containing 30% NH_4OH. When the pyroglutamyl compound (5 g) in hot ethanol (50 ml) was treated with 30% NH_4OH and the solution kept for 3 hr at room temperature, the *product* was found to be toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine amide, m.p. 212–213 °C, after crystallization from aqueous methanol, showing no m.p. depression when mixed with an authentic sample (see above). Yield 3·3 g (66%).

(vi) *Benzyloxycarbonyl*-L-*glutaminyl*-S-*benzyl*-L-*cysteine Benzyl Ester*. — Benzyloxycarbonyl-L-glutamine (5·6 g) and *S*-benzyl-L-cysteine benzyl ester *p*-toluenesulphonate (9·4 g) were dissolved in dry chloroform (50 ml) containing triethylamine (2·8 ml), and the mixture cooled to —40 °C. In a second flask were mixed triethylamine (5·6 ml), chloroform (20 ml), and phosphorus oxychloride (1·9 ml), and after cooling to —40 °C this solution was added to the first with constant swirling. The mixture was then allowed to warm to room temperature over 3 hr. The solution was washed with 3% $NaHCO_3$, the chloroform was removed, the residue was extracted with hot ethyl acetate to remove by-products, and crystallized from chloroform or methyl cyanide. Yield 3·7 g (33%), m.p. 187–190 °C (Found: C, 64·0; H, 6·1; N, 7·2; S, 5·4%. Calc. for $C_{30}H_{33}O_6N_3S$: C, 63·9; H, 5·9; N, 7·5; S, 5·7%). Harington and Mead (1936), using a different method, report m.p. 182 °C.

(vii) L-*Glutaminyl*-S-*benzyl*-L-*cysteine*.—Benzyloxycarbonyl-L-glutaminyl-*S*-benzyl-L-cysteine benzyl ester (0·5 g) was kept at 50 °C for 2 hr with 6N anhydrous HBr in acetic acid following the general method of Ben-Ishai and Berger (1952) and Ben-Ishai (1954). The peptide hydrobromide was precipitated with ether, dissolved in a small volume of dilute NH_4OH, and the pH adjusted to about 6 with acetic acid. L-*Glutaminyl*-S-*benzyl*-L-*cysteine* separated and was recrystallized from water. Yield 0·1 g, m.p. 171 °C (Found: C, 53·0; H, 6·3; N, 11·9%. Calc. for $C_{15}H_{21}O_4N_3S$: C, 53·1; H, 6·3; N, 12·4%).

(viii) *Benzyloxycarbonyl*-L-*glutaminyl*-S-*benzyl*-L-*cysteine Ethyl Ester*.—This was prepared by the phosphorus oxychloride method as described for the benzyl ester, using benzyloxycarbonyl-L-glutamine (4·0 g), *S*-benzyl-L-cysteine ethyl ester hydrochloride (3·9 g), and tetrahydrofuran in place of chloroform. Yield 2·5 g (35%), m.p. 196–198 °C, after crystallization from ethanol or dimethylformamide/ethanol (Found: C, 60·1; H, 6·3; N, 8·3%. Calc. for $C_{25}H_{31}O_6N_3S$: C, 60·0; H, 6·2; N, 8·4%). Using the mixed anhydride method the yield was even lower.

(ix) *Benzyloxycarbonyl*-L-*glutaminyl*-S-*benzyl*-L-*cysteine Hydrazide*. — The above ethyl ester (2·5 g) was dissolved in warm *n*-butanol (100 ml), 80% hydrazine hydrate (7·5 ml) was added, and the mixture kept at 40 °C for 18 hr, giving 2·0 g (82%) of the *hydrazide*, m.p. 233–234 °C, with slight decomp. after crystallization from dimethylformamide/ethanol/water (Found: C, 57·0; H, 5·9; N, 14·0%. Calc. for $C_{23}H_{29}O_5N_5S$: C, 56·6; H, 6·0; N, 14·4%).

(x) *Benzyloxycarbonyl*-L-*glutaminyl*-S-*benzyl*-L-*cysteinyl*-S-*benzyl*-L-*cysteine Ethyl Ester*.—Benzyloxycarbonyl-L-glutamine (4·9 g) and *S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteine ethyl ester (8·7 g, see below) were mixed in dry tetrahydrofuran (45 ml) containing triethylamine (2·45 ml) and the solution cooled to —40 °C in ethanol/dry ice. In a second flask phosphorus oxychloride (1·65 ml) was added slowly to tetrahydrofuran (18 ml) and triethylamine (4·85 ml) and after similar cooling, this mixture was added slowly to the first, and the whole allowed to warm to room temperature over 2 hr. The solution was made alkaline by adding with vigorous stirring an approximately equal volume of 3% $NaHCO_3$. The *product* was collected, washed with water, and dried, yielding 11·4 g (94%) of crude product, m.p. 170–175 °C. After crystallization from ethanol and then methyl cyanide, the *ester* had m.p. 181–185 °C (Found: C, 60·2; H, 6·1; O, 15·4%. Calc. for $C_{35}H_{42}O_7N_4S_2$: C, 60·5; H, 6·1; O, 16·1%). The ester (2·3 g) was converted to the *hydrazide* by dissolving in warm *n*-butanol (100 ml), adding 80% hydrazine hydrate (10 ml), and keeping at 40 °C for 18 hr. The product (1·85 g, 82%) was crystallized from dimethylformamide/ethanol/water, m.p. 227 °C (Found: C, 58·2; H, 5·9; N, 12·3%. Calc. for $C_{30}H_{40}O_6N_6S_2$: C, 57·9; H, 5·9; N, 11·7%)

(xi) *Toluene*-p-*sulphonyl*-L-*glutaminyl*-S-*benzyl*-L-*cysteinyl*-S-*benzyl*-L-*cysteine Benzyl Ester*.—The free ester from *S*-benzyl-L-cysteine benzyl ester hydrochloride (0·4 g) was added to toluene-*p*-sulphonyl-L-glutaminyl-*S*-benzyl-L-cysteine (0·5 g), diethyl hydrogen phosphite (2·0 ml), and tetraethyl pyrophosphite (0·5 ml) and the mixture warmed for 0·5 hr on a steam-bath. Dilution with water (100 ml) gave 0·8 g of a white solid, m.p. 137–153 °C, and having the odour of benzyl mercaptan. On recrystallizing several times from acetone and aqueous acetone, the m.p. rose to 176–177 °C, but the final yield was very low (Found: C, 60·3; H, 5·7; O, 14·8%. Calc. for $C_{39}H_{44}O_7N_4S_3$: C, 60·3; H, 5·7; O, 14·4%). An attempt to prepare the corresponding ethyl ester by condensing toluene-*p*-sulphonyl-L-pyroglutamyl chloride with *S*-benzyl-L-cysteinyl-*S*-benzyl-L-cysteine ethyl ester (see below) and then treating with NH_4OH gave a mixture of products from which was isolated a small amount of *3,6-di(benzylthiomethyl)-2,5-dioxopiperazine*, m.p. 174–175 °C (Found: C, 62·0; H, 5·7%. Calc. for $C_{20}H_{22}O_2N_2S_2$: C, 62·4; H, 5·7%). Hooper *et al.* (1956) also report m.p. 174–175 °C.

(d) Compounds related to the Sequence —Cy(SCH$_2$Ph).Cy(SCH$_2$Ph)—

S-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-*S*-benzyl-L-cysteine ethyl ester, m.p. 103–104 °C (hot stage), was prepared in low yield by the method of Hooper (1953, p. 157; see also Hooper *et al.* 1956), and subsequently by the better procedure of Izumiya and Greenstein (1954), except that ethyl chlorocarbonate was used in place of *iso*butyl chlorocarbonate (yield 67%), and also by the phosphorus oxychloride method with chloroform as solvent (52%). The corresponding *methyl ester* was prepared similarly from *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine (6·9 g), *S*-benzyl-L-

cysteine methyl ester hydrochloride (5·2 g), ethyl chlorocarbonate (1·9 ml), and triethylamine (2×3 ml) in chloroform. Some difficulty was encountered in effecting the initial crystallization. The product had m.p. 140 °C after several recrystallizations from ethanol. This methyl ester was also obtained by the azide method, as follows: *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine hydrazide (1·8 g, m.p. 134·5–135 °C; see Hegedüs 1948) was converted to the azide by suspending the solid in 2N HCl (5 ml) and water (20 ml) at 0 °C and treating with $NaNO_2$ (0·35 g) in water (5 ml), extracting with ether after 10 min, then washing and drying in the usual way before adding to a solution of *S*-benzyl-L-cysteine methyl ester (prepared from 1·3 g of the hydrochloride) in chloroform/ether. The product obtained after keeping the reaction mixture 2 days at 0 °C gave no m.p. depression with the methyl ester prepared by the mixed anhydride method. The yield was rather low and the product difficult to purify. It was identified by conversion to the hydrazide.

(i) S-*Benzyl*-N-*benzyloxycarbonyl*-L-*cysteinyl*-S-*benzyl*-L-*cysteine Hydrazide.* — *S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-*S*-benzyl-L-cysteine methyl or ethyl ester (2 g) and 60% aqueous hydrazine hydrate (4 ml) were kept in 2-methoxyethanol (20 ml) for 3 days at 40 °C or in *n*-butanol for 1 day at 40 °C, yielding *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-*S*-benzyl-L-cysteine hydrazide (1·6 g), m.p. 167 °C, after crystallization from methyl cyanide or methoxyethanol (Found: N, 9·9%. Calc. for $C_{28}H_{32}O_4N_4S_2$: N, 10·1%). The ethyl ester was largely unchanged on refluxing for 2 hr with hydrazine in ethanol.

(ii) S-*Benzyl*-L-*cysteinyl*-S-*benzyl*-L-*cysteine Ethyl Ester Hydrobromide.*—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-*S*-benzyl-L-cysteine ethyl ester (10·7 g) was kept for 20 min at room temperature in 7N anhydrous HBr in acetic acid (36 ml) and the *product* precipitated with ether, washed with ether and light petroleum (b.p. 40–60 °C), and recrystallized from ethanol/ether. Yield 91%, m.p. 145–147 °C (Found: S, 12·7%. Calc. for $C_{22}H_{29}O_3N_2S_2Br$: S, 12·5%).

(iii) S-*Benzyl*-N-*formyl*-L-*cysteinyl*-S-*benzyl*-L-*cysteine Methyl Ester.* — *S*-Benzyl-*N*-formyl-L-cysteine was condensed with *S*-benzyl-L-cysteine methyl ester using the ethyl chlorocarbonate mixed anhydride method. The *product* was obtained in low yield, needles from aqueous ethanol, m.p. 116–117 °C (Found: N, 5·9%. Calc. for $C_{22}H_{26}O_4N_2S_2$: N, 6·3%).

(e) *Compounds related to the Sequence —Cy(SCH₂Ph).Ala.Ser—*

(i) S-*Benzyl*-N-*benzyloxycarbonyl*-L-*cysteinyl*-L-*alanine Methyl Ester.* — This was prepared from *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteine (13·2 g) and L-alanine methyl ester hydrochloride (5·6 g) using the mixed anhydride method as described below for benzyloxycarbonyl-L-alanyl-L-serine methyl ester. The *product*, m.p. 128·5–129 °C, rosettes from ethyl acetate/light petroleum (b.p. 40–60 °C) was obtained in 80% yield (13·5 g) (Found: C, 61·5; H, 6·4; N, 6·2; CH_3O, 7·6%. Calc. for $C_{23}H_{26}O_5N_2S$: C, 61·4; H, 6·1; N, 6·5; CH_3O, 7·2%).

The corresponding *ethyl ester*, m.p. 117·5 °C, after recrystallization from aqueous ethanol, was prepared in similar fashion using L-alanine ethyl ester (Found: C, 62·3; H, 6·4; N, 5·9%. Calc. for $C_{23}H_{28}O_5N_2S$: C, 62·1; H, 6·3; N, 6·3%).

The above methyl or ethyl ester (4 g) in ethanol (50 ml) containing 60% hydrazine hydrate (4 ml), on keeping at 50 °C for 2 hr and then at room temperature for 18 hr, was converted to the corresponding *hydrazide* (3·7 g), m.p. 181 °C, needles from ethanol (Found: N, 12·7; S, 7·6%. Calc. for $C_{21}H_{26}O_4N_4S$: N, 13·0; S, 7·5%).

(ii) *Benzyloxycarbonyl*-L-*alanyl*-L-*serine Methyl Ester.*—To benzyloxycarbonyl-L-alanine (11·16 g; 0·05 mole) in dry chloroform (80 ml) at 0 °C was added triethylamine (6·6 ml) and then ethyl chlorocarbonate (4·75 ml) dropwise with shaking. The mixture was kept at 0 °C for 10 min then precooled L-serine methyl ester, previously prepared from the hydrochloride (7·78 g) and triethylamine (6·6 ml) in dry chloroform (40 ml), was added with shaking. The mixture was kept at 0 °C for 30 min and then allowed to warm to room temperature. After 2 hr the chloroform solution was washed in turn with water and aqueous $NaHCO_3$. Removal of chloroform from the dried solution, followed by addition of light petroleum (b.p. 40–60 °C), gave 51% yield of product (8·2 g), m.p. 133–134 °C, after recrystallization from ethyl acetate/light petroleum. Harris and Fruton (1951) report m.p. 134–135 °C for benzyloxycarbonyl-L-alanyl-L-serine methyl ester prepared by the azide method.

The methyl ester (8 g), on refluxing for 2 hr in ethanol (10 ml) containing 60% hydrazine hydrate (6 ml), was converted to the *hydrazide* (7·15 g), m.p. 223–224 °C (decomp.), fine needles from methoxyethanol (Found: C, 52·1; H, 6·6; N, 17·5%. Calc. for $C_{14}H_{20}O_6N_4$: C, 51·9; H, 6·3; N, 17·3%).

The methyl ester (0·6 g) with 6N HBr in glacial acetic acid gave *L-alanyl-L-serine methyl ester hydrobromide* as an oil on precipitation with ether followed by decantation and trituration with warm light petroleum (b.p. 40–60 °C).

(iii) *S-Benzyl-N-benzyloxycarbonyl-L-cysteinyl-L-alanyl-L-serine Methyl Ester.*—This was prepared by two alternative methods: (1) *S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteine (0·6 g) was reacted with L-alanyl-L-serine methyl ester hydrobromide (prepared from 0·6 g of the benzyloxycarbonyl compound) by the mixed anhydride method using ethyl chlorocarbonate. The *product* was crystallized from ethanol and then from methanol giving small rosettes, m.p. 195–196 °C (Found: C, 57·8; H, 6·1; N, 7·9; S, 6·5; CH_3O, 6·0%. Calc. for $C_{25}H_{31}O_7N_3S$: C, 58·0; H, 6·1; N, 8·1; S, 6·2; CH_3O, 6·0%. In a preliminary experiment this ester was obtained in a metastable form, small needles, m.p. 146–147 °C (Found: C, 58·2; H, 6·2; N, 7·5; CH_3O, 6·1; S, 5·9%).

The methyl ester (0·7 g), on keeping for 3 days at 35 °C with 60% hydrazine hydrate (0·7 ml) in 2-methoxyethanol (10 ml), gave the *hydrazide* (0·5 g), m.p. 208–209 °C, after recrystallization from 2-methoxyethanol (Found: N, 12·9; S, 6·0%. Calc. for $C_{24}H_{31}O_6N_5S$: N, 13·5; S, 6·2%).

(2) A solution of *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-alanine hydrazide (1·25 g; 0·003 mole) in a mixture of glacial acetic acid (5 ml), 2N HCl (4 ml) and water (10 ml) was cooled to 0 °C, and a cold solution of $NaNO_2$ (0·22 g) in water added dropwise with shaking. After 2 min the precipitated azide was extracted with cold ethyl acetate (50 ml), and the extract washed with ice-water and then with ice-cold aqueous $NaHCO_3$, then dried (Na_2SO_4) at 0 °C. The latter part of the experiment was carried out in a cold room at 2 °C. The filtered azide solution was kept at 2 °C for 2 days with a solution of L-serine methyl ester prepared by dissolving L-serine methyl ester hydrochloride (0·42 g) and triethylamine (0·4 ml) in chloroform (5 ml), then adding ethyl acetate, and filtering off the precipitated triethylamine hydrochloride. The greater part of the product which had crystallized was collected, the remainder being obtained by concentrating the filtrate after washing to remove acidic and basic impurities (total yield 1·1 g, 73%). It had m.p. 195–196 °C on recrystallization from ethanol and then from methanol, no depression being observed on admixture with the product obtained by method (1).

If the above conditions are not strictly adhered to, the yield is reduced by decomposition of the azide to the corresponding amide. This is sparingly soluble in ethyl acetate, and usually separates during the early stages of the experiment or during the drying with sodium sulphate. The following experiment illustrates its ease of formation.

(iv) *S-Benzyl-N-benzyloxycarbonyl-L-cysteinyl-L-alanine Amide.* — *S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-alanine hydrazide (0·5 g) was shaken with water (5 ml), 2N HCl (5 ml), and ethyl acetate (5 ml). The material was observed to change in crystalline form to the hydrazide hydrochloride. $NaNO_2$ (0·2 g) in water was added dropwise with shaking to give a clear mixture. After 2 min crystals commenced to form and were collected after 5 min and recrystallized from ethanol, giving the amide, m.p. 181 °C (Found: N, 10·0; S, 7·7%. Calc. for $C_{21}H_{25}O_4N_3S$: N, 10·1; S, 7·7%). No depression in m.p. was observed on admixture with the product, m.p. 181 °C, obtained on keeping *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-alanine ethyl ester in methanolic ammonia for 3 days at room temperature.

(f) Compounds related to the Sequence —Cy(SCH_2Ph).Ala.Ser.Val.Cy(SCH_2Ph)—

(i) *Benzyloxycarbonyl-L-valyl-S-benzyl-L-cysteine Benzyl Ester.* — Benzyloxycarbonyl-L-valine (4·7 g) was reacted with *S*-benzyl-L-cysteine benzyl ester (from 9·0 g of the toluene-*p*-sulphonate) in chloroform by the mixed anhydride method using ethyl chlorocarbonate (1·8 ml) and triethylamine (2×2·6 ml). On keeping the reaction mixture at 0–10 °C for 30 min the *product* crystallized. The mixture was kept at room temperature for 18 hr and ether (50 ml) was added. The product was collected and washed in turn with ether, aqueous $NaHCO_3$, and water, giving 7·6 g, m.p. 155–158 °C (76%). The product crystallized from benzene as needles,

m.p. 157–158 °C (Found : C, 67·3 ; H, 6·4 ; N, 5·0%. Calc. for $C_{29}H_{34}O_5N_2S$: C, 67·4 ; H, 6·4 ; N, 5·2%).

The benzyloxycarbonyl group was removed using 3N anhydrous HBr in acetic acid at room temperature, giving L-valyl-*S*-benzyl-L-cysteine benzyl ester hydrobromide, m.p. 195–197 °C, needles from water, in 67% yield (Found : C, 55·4 ; H, 6·2 ; N, 5·3 ; O, 10·0%. Calc. for $C_{22}H_{29}O_3N_2SBr$: C, 54·9 ; H, 6·1 ; N, 5·8 ; O, 10·0%). In another experiment (cf. Ben-Ishai 1954) the benzyloxycarbonyl benzyl ester (1 g) was heated on the steam-bath with 2N anhydrous HBr in acetic acid (20 ml) for 1 hr, and the solvent removed under vacuum. Ethanol (40 ml) was then added and evaporated. The residue was dissolved in NH_4OH, boiled for a short time, then cooled, giving *L-valyl-S-benzyl-L-cysteine monohydrate* (0·5 g, yield 81%), m.p. 193–196 °C, rosettes from water (Found : C, 54·8 ; H, 8·0 ; N, 7·6 ; O, 20·2%. Calc. for $C_{15}H_{22}O_3N_2S.H_2O$: C, 54·8 ; H, 7·4 ; N, 8·5 ; O, 19·5%). The loss in weight of the hydrate on prolonged drying amounted to 6·1% (Calc. for monohydrate : 5·5%).

(ii) *Benzyloxycarbonyl-L-alanyl-L-seryl-L-valyl-S-benzyl-L-cysteine Benzyl Ester.* — This was prepared by the " azide method " as described for *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-alanyl-L-serine methyl ester, using benzyloxycarbonyl-L-alanyl-L-serine hydrazide (0·19 g) and L-valyl-*S*-benzyl-L-cysteine benzyl ester hydrobromide (0·29 g). The product (0·3 g, 74%) had m.p. 187–188 °C after two recrystallizations from ethanol (Found : C, 61·8 ; H, 6·6 ; N, 7·8%. Calc. for $C_{36}H_{44}O_6N_4S$: C, 62·4 ; H, 6·4 ; N, 8·1%).

The benzyloxycarbonyl group was removed by keeping the ester (2·0 g) in 6N HBr in acetic acid at room temperature, and the product was twice recrystallized from ethanol/light petroleum (b.p. 40–60 °C) giving *L-alanyl-L-seryl-L-valyl-S-benzyl-L-cysteine benzyl ester hydrobromide* (0·9 g), m.p. 180–182 °C, crystals from dimethylformamide/acetone/light petroleum (b.p. 40–60 °C) (Found : S, 4·8%. Calc. for $C_{28}H_{39}O_6N_4SBr$: S, 5·0%). Addition of more light petroleum to the mother liquors gave a small amount of a diastereoisomer, m.p. 198–200 °C (Found : S, 4·8%).

(iii) *S-Benzyl-N-benzyloxycarbonyl-L-cysteinyl-L-alanyl-L-seryl-L-valyl-S-benzyl-L-cysteine Benzyl Ester.*—This was prepared by the " azide method " from *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinyl-L-alanyl-L-serine hydrazide (0·3 g) and L-valyl-*S*-benzyl-L-cysteine benzyl ester hydrobromide (0·28 g). The product, m.p. 200–202 °C, was obtained as a microcrystalline powder from ethanol (Found : C, 61·5 ; H, 6·4 ; O, 16·5%. Calc. for $C_{46}H_{55}O_9N_5S_2$: C, 62·3 ; H, 6·3 ; O, 16·3%).

(g) Compounds related to the Sequence —Leu.Cy(SCH$_2$Ph).Gly—

(i) *S-Benzyl-N-benzyloxycarbonyl-L-cysteinylglycine Ethyl Ester and Hydrazide.*—*S*-Benzyl-*N*-benzyloxycarbonyl-L-cysteine (10 g) was coupled with glycine ethyl ester (from 4 g of the hydrochloride) using the ethyl chlorocarbonate mixed anhydride method. The reaction mixture was kept at —5 °C for 10 min, then at room temperature overnight, and was finally heated at 60 °C for 15 min. The yield was 9 g (72%), m.p. 99–100 °C, after crystallization from ethanol/light petroleum (b.p. 40–60 °C), $[\alpha]_D^{22}$ —39·7° (*c*, 4·32 in dioxan), $[\alpha]_D^{20}$ —28·7° (*c*, 5·83 in glacial acetic acid). Hooper *et al.* (1956) record $[\alpha]_D^{20}$ —39·6° (*c*, 4·32 in dioxan), Goldschmidt and Jutz (1953) found $[\alpha]_D^{20}$ —26·8°, and Wieland and Heinke (1956), $[\alpha]_D^{27}$ —28·2° (both *c*, 6 in acetic acid). The ester was converted to the hydrazide at 0 °C following Lautsch and Kraege (1956). Three recrystallizations from ethanol gave a product, m.p. 142 °C, $[\alpha]_D^{19}$ —14·8° (*c*, 0·96 in EtOH). The same product was also obtained on keeping the ester (2 g) and 80% hydrazine hydrate (1·1 ml) in *n*-butanol (20 ml) at 40 °C for 18 hr. Hooper *et al.* (1956) record m.p. 142 °C, $[\alpha]_D^{24}$ —18·1° (*c*, 0·17 in EtOH) for *S*-benzyl-*N*-benzyloxycarbonyl-L-cysteinylglycine hydrazide obtained by refluxing the ester with alcoholic hydrazine, whilst Lautsch and Kraege (1956) report m.p. 142 °C, $[\alpha]_D^{23}$ —38·4±2° (*c*, 0·94 in absolute EtOH). This latter rotation would seem to be in error. In an early attempt to prepare this hydrazide, the ethyl ester was refluxed 5 hr with methanolic hydrazine when the main product proved to be dibenzyl disulphide, m.p. and mixed m.p. 70–71 °C (Found : C, 68·1 ; H, 5·9%. Calc. for $C_{14}H_{14}S_2$: C, 68·2 ; H, 5·7%), together with a small amount of the hydrazide.

(ii) *S-Benzyl-N-benzyloxycarbonyl-L-cysteinylglycine Benzyl Ester.*—This was prepared by the mixed anhydride method as described above for the ethyl ester. Yield 77%, m.p. 127–128 °C

after crystallization from aqueous ethanol (Found: C, 65·8; H, 5·7; N, 5·2%. Calc. for $C_{27}H_{28}O_5N_2S$: C, 65·8; H, 5·7; N, 5·7%); $[\alpha]_D^{19}$ −28·3° (*c*, 0·98 in acetone).

(iii) S-*Benzyl*-L-*cysteinylglycine Benzyl Ester Hydrobromide*.—The above ester (1·05 g) was dissolved in anhydrous 5N HBr in acetic acid (3·4 ml) and allowed to stand for 15 min. Dry ether (90 ml) was added and the granular product collected and washed with dry ether. Yield 0·75 g (80%), m.p. 124 °C (Found: N, 6·8; Br, 20·7%. Calc. for $C_{19}H_{23}O_3N_2SBr$: N, 6·4; Br, 18·2%). These analytical results did not improve after recrystallization from ethanol/ether or acetone/ether, and the crude product was used in the next step without purification.

(iv) *Benzyloxycarbonyl*-L-*leucyl*-S-*benzyl*-L-*cysteinylglycine Benzyl Ester*.—Benzyloxycarbonyl-L-leucine (1·99 g) was coupled with *S*-benzyl L-cysteinylglycine benzyl ester (from 3·0 g of the crude hydrobromide) using the mixed anhydride method with ethyl chlorocarbonate in chloroform solution. After keeping the reaction mixture at 45–50 °C for 30 min, the crude product was isolated in 50% yield and recrystallized from aqueous acetone as colourless microcrystals, m.p. 151–152 °C (Found: C, 64·9; H, 6·5; N, 6·9%. Calc. for $C_{33}H_{39}O_6N_3S$: C, 65·4; H, 6·5; N, 6·9%).

(v) L-*Leucyl*-S-*benzyl*-L-*cysteinylglycine*.—The above ester (1 g) was heated with 5N HBr in acetic acid at 40–50 °C for 2 hr and the reaction mixture was then evaporated in a vacuum. The resulting orange oil solidified after trituration with dry ether (100 ml) and was then filtered and dissolved in water (15 ml). The aqueous solution was brought to pH 7 with $NaHCO_3$ and the crude product (0·43 g, 68%), m.p. 176–180 °C, crystallized from water as colourless rosettes, m.p. 185 °C (decomp.), which gave a positive reaction with ninhydrin (Found: C, 56·1; H, 7·3; N, 10·7%. Calc. for $C_{18}H_{27}O_4N_3S$: C, 56·7; H, 7·1; N, 11·0%); $[\alpha]_D^{20}$ −9·7° (*c*, 1 in N HCl).

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AMINO ACIDS AND PEPTIDES*

V. THE ALKALINE SAPONIFICATION OF N-BENZYLOXYCARBONYL PEPTIDE ESTERS

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Summary

In the alkaline saponification at room temperature of six *N*-benzyloxycarbonyl peptide esters (I) different products were obtained depending on the amount of alkali employed. When 1 mole of alkali was used, all the esters gave the corresponding acids, although with benzyloxycarbonylglycyl-*S*-benzyl-L-cysteine ethyl ester some racemization occurred. With 2 moles of alkali, benzyl alcohol was eliminated from the benzyloxycarbonyl group in all esters where a glycine residue was next to the *N*-terminal residue, thereby forming either the corresponding urea derivative (III) or the hydantoin-3-acetic acid derivative (II). Excess alkali caused no similar rearrangement in other sequences under these conditions.

The need for special care in saponifying certain *N*-benzyloxycarbonyl peptide sequences is indicated. An improvement in the tetraethyl pyrophosphite procedure for the synthesis of peptides is described.

I. INTRODUCTION

The alkaline saponification of *N*-benzyloxycarbonyl peptide esters is a procedure in peptide synthesis in which poor yields are often encountered. In some experiments on the room temperature alkaline saponification of benzyloxycarbonylglycylglycine ethyl ester (I; R^1=H, R^2=H) it has now been observed that the yield of benzyloxycarbonylglycylglycine decreases with increasing amounts of alkali in excess of one equivalent and with increasing saponification time. A second product, which is water-soluble, has been isolated and shown to be carbonyl bis-*N*-glycine (III; R^1=H, R^2=H), arising by elimination of benzyl alcohol from the benzyloxycarbonyl dipeptide. Urea derivatives of this kind have been prepared previously by heating *N*-methoxycarbonyl or *N*-ethoxycarbonyl dipeptides or their esters with 2 equivalents of N sodium hydroxide for several hours (Fischer 1903*a*; Wessely, Schlögl, and Korger 1952, and earlier work referred to therein) and very recently from *N*-benzyloxycarbonyl dipeptide esters by heating for 2–3 hr with 2 equivalents of 0·1N sodium hydroxide in aqueous ethanol (Schlögl, Wessely, and Woidich 1956). It has been shown that the intermediate in this type of rearrangement is the hydantoin-3-acetic acid derivative (II) (Wessely, Schlögl, and Wawersich 1952). In addition, several *N*-benzyloxycarbonyl dipeptide esters have been

* For Part IV of this series see Maclaren, Savige, and Swan (1958).

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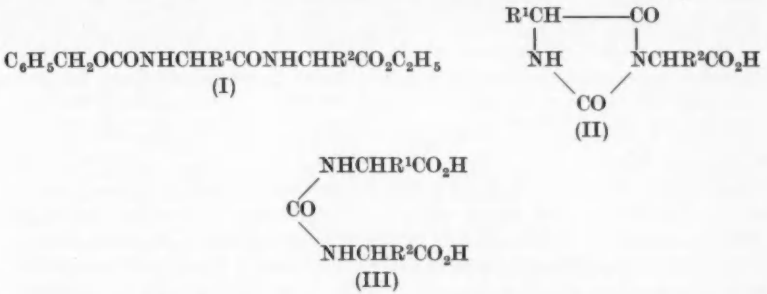
converted to hydantoin-3-acetamides by treatment with ammonia (Fruton and Bergmann 1942; Dekker, Taylor, and Fruton 1949). Cohen and Fry (1956) have shown that the action of alcoholic sodium ethoxide on benzyloxycarbonyl dipeptide acids, esters, and amides at room temperature is a general method for preparing the corresponding derivatives of hydantoin-3-acetic acid.



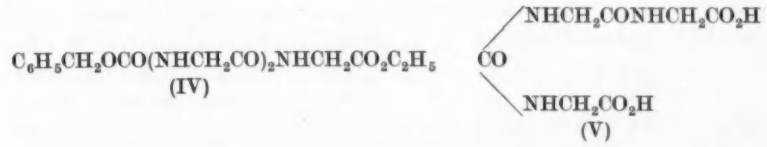
Although this reaction has been widely studied already, the observation that it can take place in high yield under mild conditions (e.g. at room temperature with 2 moles of 0·1N alkali) was surprising and led us to try other dipeptide derivatives.

II. Materials

Most of the *N*-benzyloxycarbonyl peptide esters were prepared using the tetraethyl pyrophosphite reagent of Anderson, Blodinger, and Welcher (1952). It is now found that the yields by this procedure are greatly increased when anhydrous pyridine is used as solvent instead of the usual diethyl phosphite.

III. Results

Saponification of benzyloxycarbonylglycylglycine ethyl ester in 1 equivalent of 0·5N sodium hydroxide at room temperature gave the expected acid in 85 per cent. yield. Using 2 equivalents, acidification after 1 hr gave benzyloxycarbonylglycylglycine (47 per cent.) and carbonyl-bis-*N*-glycine (36 per cent.); acidification after 5 hr gave only carbonyl bis-*N*-glycine (74 per cent.). Benzyloxycarbonyldiglycylglycine ethyl ester (IV) with 1 equivalent of 0·1N alkali for



1 hr gave the corresponding acid (63 per cent.); 2 equivalents for 5 hr gave carbonyl-*N*-glycine-*N'*-glycylglycine (V) (65 per cent.). This product is probably identical with the alleged *N*-carboxydiglycylglycine described by Fischer (1903*b*).

Benzyloxycarbonylglycyl-DL-leucine ethyl ester (I; R^1=H, R^2=$-CH_2CH(CH_3)_2$) was hydrolysed to the corresponding acid by either

1 or 2 equivalents of alkali, and benzyloxycarbonyl-L-leucylglycine ethyl ester (I; $R^1 = -CH_2CH(CH_3)_2$, $R^2 = H$) likewise gave the corresponding acid (78 per cent.) with 1 equivalent of alkali, but with 2 equivalents the product which separated after acidification and storage at 0 °C was 5-*iso*butylhydantoin-3-acetic acid (II; $R^1 = -CH_2CH(CH_3)_2$, $R^2 = H$). In this case presumably the unsymmetrical urea (III) cyclizes to the hydantoin under much milder conditions than usual (see Cohen and Fry 1956; Schlögl, Wessely, and Woidich 1956, and other references quoted therein), or alternatively, the second equivalent of alkali induces hydantoin formation but fails then to open the hydantoin ring to form the urea.

With *N*-benzyloxycarbonylglycyl-*S*-benzyl-L-cysteine ethyl ester a different result was found. Using either 1 or 2 equivalents of alkali in aqueous ethanol, the product was a mixture of *N*-benzyloxycarbonylglycyl-*S*-benzyl-L-cysteine and *N*-benzyloxycarbonylglycyl-*S*-benzyl-DL-cysteine with none of the hydantoin or urea products. Racemization probably occurs prior to saponification since *N*-benzyloxycarbonylglycyl-*S*-benzyl-L-cysteine could be recovered unchanged from comparable alkaline solutions. This is in accord with a β-elimination mechanism for the racemization (Neuberger 1948); conversion of the ester group to carboxylate anion would be expected to retard ionization of the α-hydrogen atom, the essential first step in β-elimination. *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteinylglycine ethyl ester gave the corresponding acid when hydrolysed with 1 equivalent of alkali; with 2 equivalents 5-benzylthiomethylhydantoin-3-acetic acid (II; $R^1 = -CH_2\text{-}S\text{-}CH_2C_6H_5$, $R^2 = H$) was isolated, and also some dibenzyl disulphide, presumably resulting from β-elimination of toluene-ω-thiol and subsequent aerial oxidation (cf. Maclaren, Savige, and Swan 1958).

IV. Discussion

From these results it is clear that the nature of the R^1 group is unimportant, but the R^2 group exerts a decisive influence on the ease of rearrangement and under the conditions used in this work (2 equiv. of alkali at room temperature), elimination of benzyl alcohol and hydantoin formation occur only when the R^2 group is H. However, under vigorous conditions this elimination can be effected with all alkoxycarbonyl polypeptides (Wessely, Schlögl, and Korger 1952). The poor yields sometimes reported in the literature for alkaline saponification of *N*-benzyloxycarbonyl peptide esters (e.g. Harris and Fruton 1951; Roberts 1954) may be due to decompositions of this type, since unlike the benzyloxycarbonyl peptides, the urea and hydantoin derivatives are water-soluble and hence are not precipitated in the final acidification step. The need for special care is indicated in alkali treatment of *N*-benzyloxycarbonyl peptides where a glycine residue is next to the *N*-terminal residue.

V. Experimental

Melting points are uncorrected. Analyses are by the C.S.I.R.O. Microanalytical Laboratory.

The preparation of the various *N*-benzyloxycarbonylamino acids and amino acid ethyl ester hydrochlorides is described in an earlier paper (Maclaren, Savige, and Swan 1958).

(a) Preparation of N-Benzyloxycarbonyl Peptide Esters

The following is adapted from the "standard" procedure of Anderson, Blodinger, and Welcher (1952).

The *N*-benzyloxycarbonylamino acid (0·01 mole) and the amino acid ethyl ester hydrochloride (0·01 mole) were suspended in the anhydrous solvent (50 ml of either pyridine or diethyl phosphite), tetraethyl pyrophosphite (5 ml), prepared by Maclaren's (1955) method, was added with shaking (if diethyl phosphite was used as solvent) then triethylamine (0·01 mole) was also added, and the mixture protected by a drying tube was heated on the steam-bath for 1 hr. After the solvent had been removed under vacuum at approximately 50 °C, the residue was diluted with water (100 ml) and ethyl acetate (100 ml). The ethyl acetate layer was washed successively with saturated $NaHCO_3$ soln. (50 ml), N HCl (50 ml), and water (50 ml), and then dried over Na_2SO_4. After filtration the solvent was evaporated and the residue recrystallized from benzene-light petroleum (b.p. 40–60 °C) or from aqueous ethanol.

Benzyloxycarbonylglycylglycine ethyl ester (I; R^1=H, R^2=H), m.p. 81–83 °C, was obtained in 77% yield in pyridine as compared with 58% in diethyl phosphite; Süs and Hoffmann (1951) report m.p. 82·5–83 °C.

Benzyloxycarbonyldiglycylglycine ethyl ester (IV), m.p. 166–168 °C, was obtained in 43% yield in diethyl phosphite, from benzyloxycarbonylglycine and the dipeptide ester hydrochloride; Fruton, Smith, and Driscoll (1948) report m.p. 165 °C.

N - Benzyloxycarbonylglycyl - *S* - benzyl - L - cysteine ethyl ester (I; R^1=H, R^2=$-CH_2-S-CH_2C_6H_5$), m.p. 81–83 °C, was obtained in 86% yield in pyridine; Hooper *et al.* (1956) report m.p. 80 °C.

N - Benzyloxycarbonyl - *S* - benzyl - L - cysteinylglycine ethyl ester (I; R^1=$-CH_2-S-CH_2-C_6H_5$, R^2=H), m.p. 98–100 °C, was obtained in 78% yield in pyridine as compared with 53% in diethyl phosphite; Hooper *et al.* (1956) report m.p. 94 °C.

Samples of benzyloxycarbonyl-L-leucylglycine ethyl ester and benzyloxycarbonylglycyl-DL-leucine ethyl ester were kindly supplied respectively by Dr. J. M. Swan and Mr. I. W. Stapleton of these laboratories.

(b) Saponification of Benzyloxycarbonylglycylglycine Ethyl Ester (I; R^1=R^2=H)

The ester (1·5 g; 0·005 mole) was suspended in 0·5N NaOH (11 ml; 0·005 mole) and shaken mechanically until solution was complete. Acidification yielded (1·1 g, 85%) benzyloxycarbonylglycylglycine (II; R^1=R^2=H), m.p. 177–178 °C, alone and admixed with an authentic sample.

The ester (1·5 g; 0·005 mole) was suspended in 0·5N NaOH (23 ml; 0·011 mole) and shaken until solution was complete, then kept at room temperature for a total of 5 hr. After acidification the soln. was cooled to 0 °C and slowly deposited a crystalline precipitate (0·55 g) which was filtered and washed with a small volume of cold water, m.p. 186 °C (decomp.). Evaporation of the filtrate and washings gave a second crop (0·1 g), m.p. 188 °C (decomp.), total yield 74%. Recrystallization from water gave carbonyl bis-*N*-glycine (III; R^1=R^2=H), m.p. 193–194·5 °C (decomp.); Wessely and Kemm (1928) report m.p. 204–206 °C (decomp.) (Found: C, 34·3; H, 4·8; N, 15·9%; equiv. wt., 88·0. Calc. for $C_5H_8O_5N_2$: C, 34·1; H, 4·6; N, 15·9%; equiv. wt., 88·1). The mixture of products obtained when the hydrolysis soln. was acidified after 1 hr, was separated by extraction with warm water and yielded 47% benzyloxycarbonylglycylglycine and 36% carbonyl bis-*N*-glycine.

(c) Saponification of Benzyloxycarbonyldiglycylglycine Ethyl Ester (IV)

The ester (0·35 g; 0·001 mole) was saponified with 0·1N NaOH (11 ml; 0·0011 mole) exactly as described above. Acidification after 1 hr yielded benzyloxycarbonyldiglycylglycine (V) (0·2 g, 63%), m.p. 196–197 °C; Bergmann, Zervas, and Fruton (1935) report m.p. 196 °C.

Saponification under the same conditions using 0·1N NaOH (21 ml; 0·0021 mole) for 5 hr, gave no water-insoluble product on acidification, but evaporation of the soln. in a vacuum gave a solid residue. This was recrystallized from a small vol. of water yielding *carbonyl-N-glycine-*

N'-glycylglycine (*V*), m.p. 205–206 °C (0·15 g, 65%); Fischer (1903*b*) reports " carboxy diglycylglycine ", m.p. 210 °C (Found: C, 36·4; H, 4·9; N, 18·2%; equiv. wt., 116·2. Calc. for $C_7H_{11}O_6N_3$: C, 36·1; H, 4·8; N, 18·0%; equiv. wt., 116·6).

(*d*) *Saponification of Benzyloxycarbonylglycyl-*DL*-leucine Ethyl Ester* (*I*; R^1=*H*, R^2=$-CH_2CH(CH_3)_2$)

The ester (0·35 g; 0·001 mole) was dissolved in ethanol (10 ml) and N NaOH (1·1 ml; 0·0011 mole) was added. After 16 hr the soln. was evaporated in a vacuum and the residue dissolved in water (10 ml) and acidified with HCl. The crude product (0·25 g, 78%) was recrystallized as long colourless needles of *benzyloxycarbonylglycyl-*DL*-leucine*, m.p. 126–127 °C (Found: C, 59·6; H, 7·1; N, 8·5%; equiv. wt., 322·1. Calc. for $C_{16}H_{22}O_5N_2$: C, 59·6; H, 6·9; N, 8·7%; equiv. wt., 322·4). The same product was isolated when the saponification was carried out with 2 moles of alkali at room temp. for 3 days.

(*e*) *Saponification of Benzyloxycarbonyl-*L*-leucylglycine Ethyl Ester* (*I*; R^1=$-CH_2CH(CH_3)_2$, R^2=*H*)

Using the general method given previously, saponification with 1 mole NaOH in methanol for 3 days gave benzyloxycarbonyl-L-leucylglycine (78% theory) as colourless prisms, m.p. 112–114 °C; Bergmann, Zervas, and Fruton (1935) report m.p. 115 °C.

When the saponification was carried exactly as above using 2 moles NaOH, the acidified soln. when kept at 0 °C slowly deposited 5-*iso*butylhydantoin-3-acetic acid (II; R^1=$-CH_2CH(CH_3)_2$, R^2=H) (76% theory) which crystallized from water as colourless prisms, m.p. 180–180·5 °C (Found: C, 50·5; H, 6·4; N, 13·0%; equiv. wt., 211. Calc. for $C_9H_{14}O_4N_2$: C, 50·5; H, 6·6; N, 13·1%; equiv. wt., 214); Wessely, Schlögl, and Korger (1952) report m.p. 183–185 °C.

(*f*) *Saponification of* N-*Benzyloxycarbonylglycyl-*S*-benzyl-*L*-cysteine Ethyl Ester* (*I*; R^1=*H*, R^2=$-CH_2-S-CH_2C_6H_5$)

The ester (0·86 g; 0·002 mole) was dissolved in ethanol (20 ml) and N NaOH (2·1 ml; 0·002 mole) and kept at room temp. 15 hr. The soln. was then evaporated under vacuum and the residue dissolved in water (25 ml) and acidified with conc. HCl (0·3 ml). The slightly gummy product was filtered and fractional crystallization from aqueous ethanol gave as the less-soluble product N-*benzyloxycarbonylglycyl-*S*-benzyl-*DL*-cysteine* as colourless plates, m.p. 141–143 °C (0·3 g, 37% theory), $[\alpha]_D^{18}$ 0 (*c*, 1·1 in acetone) (Found: C, 59·9; H, 5·8; O, 20·0; N, 6·8%. Calc. for $C_{20}H_{22}O_5N_2S$: C, 59·7; H, 5·5; O, 19·9; N, 7·0%). The more-soluble fraction was the isomeric *N*-benzyloxycarbonylglycyl-*S*-benzyl-L-cysteine, long colourless needles, m.p. 120–121 °C (0·3 g, 37% theory) (Found: C, 60·0; H, 5·9; O, 19·7; N, 6·8%) $[\alpha]_D^{18}$ —24° (*c*, 1·2 in EtOH); Hooper *et al.* (1956) report m.p. 117 °C, $[\alpha]_D^{19}$ —65° (*c*, 0·08 in EtOH). (The author was unable to make accurate measurements at this latter concentration.) Under the same conditions using 2 moles of NaOH racemization occurred to approximately the same extent, whereas if *N*-benzyloxycarbonylglycyl-*S*-benzyl-L-cysteine was likewise treated with 2 moles of alkali, no racemic product could be isolated.

(*g*) *Saponification of* N-*Benzyloxycarbonyl-*S*-benzyl-*L*-cysteinylglycine Ethyl Ester* (*I*; R^1=$-CH_2-S-CH_2-C_6H_5$, R^2=*H*)

When the ester was saponified with 1 mole NaOH in ethanol for 5 hr and worked up under the usual conditions, *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteinylglycine was obtained which separated as a colourless granular solid from aqueous acetic acid, m.p. 88–90 °C; $[\alpha]_D^{20}$ —33° (*c*, 0·5 in EtOH). The product showed a great tendency to gel in all solvents and hence was difficult to purify (Found: C, 59·2; H, 5·6; N, 6·6; S, 7·9%. Calc. for $C_{20}H_{22}O_5N_2S$: C, 59·7; H, 5·5; N, 7·0; S, 8·0%). This product has been prepared previously by different methods; Hooper *et al.* (1956) report m.p. 153–154 °C, $[\alpha]_D^{20}$ —11·4° (*c*, 2·6 in EtOH), whereas Wieland and Weidenmüller (1955) report m.p. 94–96 °C, $[\alpha]_D^{18}$ —35° (*c*, 2 in EtOH). Earlier papers by Hegedüs (1948) and by Consden and Gordon (1950) support the latter set of physical constants,

as do the results given above. In one saponification run a second acid was isolated in small yield as colourless needles from aqueous ethanol, m.p. 180–181 °C (Found: C, 57·2; H, 5·5; N, 6·4; S, 7·3%; equiv. wt., 379) but so far no structure has been assigned to this minor product.

The ester (1·72 g; 0·004 mole) was saponified by N NaOH (8·2 ml) in ethanol (40 ml) for 18 hr at room temp. The reaction mixture was evaporated in a vacuum, and the residue suspended in water and extracted with ether. Evaporation of the ether extract and recrystallization from aqueous ethanol yielded colourless needles of dibenzyl disulphide (0·1 g), m.p. 70–71 °C, alone and admixed with a pure specimen. The aqueous layer was acidified and deposited a gum, which was extracted repeatedly with boiling water. Evaporation of the aqueous extract gave colourless needles of 5-benzylthiomethylhydantoin-3-acetic acid (II; R^1=—CH_2—S—CH_2—C_6H_5, R^2=H) (0·25 g, 21% theory), m.p. 154–155 °C (Found: C, 52·9; H, 5·0; N, 8·9; S, 11·2%. Calc. for $C_{13}H_{14}O_4N_2S$: C, 53·1; H, 4·8; N, 9·5; S, 10·9%); Schlögl, Wessely, and Woidich (1956) report m.p. 153–154 °C.

VI. Acknowledgment

The author gratefully acknowledges the valuable advice of Dr. J. M. Swan.

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THE STEREOCHEMISTRY AND HOFMANN DEGRADATION OF LUPININE METHIODIDES

By W. D. Crow*

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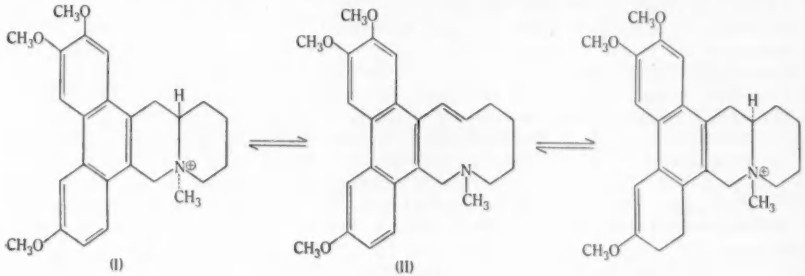
Summary

Optical rotation studies on the epimers (—)-lupinine and (+)-*epi*lupinine and their methiodides lead to the conclusion that while (+)-*epi*lupinine methiodide has the normal *trans*-ring junction, (—)-lupinine methiodide has a *cis*-ring junction.

Unlike the quaternary salts of cryptopleurine, canadine, and tetrahydropalmatine, neither of the lupinine methiodides could be racemized by refluxing with alkali.

I. Introduction

The isomerization of cryptopleurine methiodide (I) by alkali to *iso*cryptopleurine methiodide has recently been shown (Gellert 1956) to involve only racemization at the 9- and 10-positions of the quinolizidine nucleus (i.e. *iso*cryptopleurine methiodide is actually *dl*-cryptopleurine methiodide), and it has been suggested that the reaction proceeds through the labile intermediate II. Both tetrahydropalmatine and canadine methiodides (III and IV respectively) also



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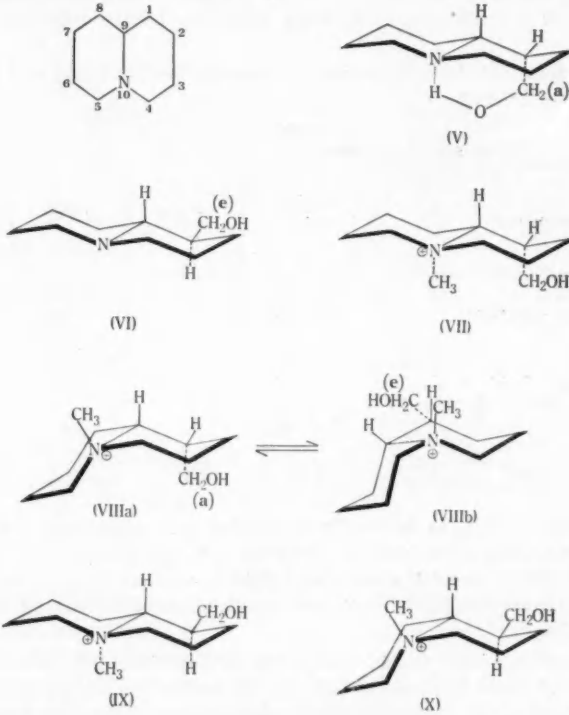
undergo this type of racemization ; in the latter case the methine base analogous to II was isolated (Pyman 1913) but reverted on standing to the quaternary salt. Since these three alkaloids are unsaturated quinolizidine derivatives, it was of interest to determine whether racemization could be similarly induced in the fully saturated quinolizidine molecule. Such a reaction could prove useful in the study of other groups of alkaloids containing the quinolizidine ring system. The epimeric 1-hydroxymethylquinolizidines, (−)-lupinine (V) and (+)-*epi*lupinine (VI), are suitable compounds for examination, since much of their stereochemistry is known.



II. Stereochemistry of the Lupinines and their Methiodides

The fact that (−)-lupinine (V) and (+)-*epi*lupinine (VI) are epimers at C_1 was recognized by Winterfeld and Holzschneider (1931), and Cookson (1953) pointed out that it is reasonable to assume that the more stable (+)-*epi*lupinine is the epimer containing the equatorial hydroxymethyl group. This has been confirmed by Ratusky, Reiser, and Sorm (1954), by Galinovsky and Nesvadba (1954), and by Thomas, Vipond, and Marion (1955) by examination of the dipole moments, internal quaternization of the *p*-toluenesulphonyl esters, and infra-red spectra respectively. Each base is theoretically capable of forming two meth-

iodides, depending upon whether the carbonium ion adds to give a *cis*- or a *trans*-ring junction. The *trans*-compounds (VII and IX) would normally be expected to be formed almost exclusively, being energetically more favoured than the *cis* (VIIIa and X), but examination of models indicated that this may not be the case with lupinine methiodide. The axial hydroxymethyl group in VII encounters considerable interference from the axial substituents on C_3, N, and C_8, whereas in the *cis*-joined VIIIa the interference can be avoided by a conformational change to VIIIb in which the hydroxymethyl group is equatorial. If lupinine methiodide is correctly represented by VIIIb then, as would be expected, the attack by the carbonium ion must have been preferentially directed to the face of the nitrogen atom away from the hydrogen-bonded hydroxyl group.

Optical rotations were determined in water (*c*, 1–5 per cent.) and the results are set out in Table 1.

TABLE 1

MOLECULAR ROTATIONS OF LUPININE DERIVATIVES

Compound	Melting Point (°C)	$[\alpha]_D^{20}$	$[M]_D$	$\Delta[M]_D$*
(+)-*epi*Lupinine	77–78	+38°	+64°	
(+)-*epi*Lupinine methiodide ..	252–253	+6°	+19°	+45°
(—)-Lupinine	43–44	—21°	—35°	—66°
(—)-Lupinine methiodide	296–297	+10°	+31°	
(—)-Lupinine ethoxycarbonylmethiodide	160–162	+11°	+42°	—77°

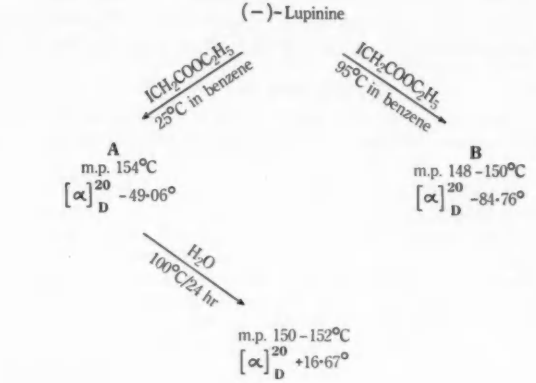
*$\Delta[M]_D = [M]_{D\ base} - [M]_{D\ salt}$.

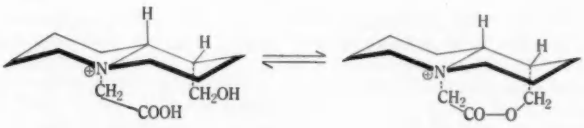
The change in $[M]_D$ in passing from lupinine to its methiodide is of opposite sign and similar magnitude to that observed with *epi*lupinine; in view of the proximity of the asymmetric centres complete agreement is not to be expected, but the results are consistent with the representations VIIIb and IX for the two methiodides.

Fodor, Sallay, and Dutka (1957) have described the formation from (—)-lupinine of three quaternary salts by the action of iodoacetic ester. The formation of the salts is outlined below. The compounds were not recrystallized, and no mixed melting points were reported.

The purpose behind this scheme was to establish the stereochemistry of lupinine by internal cyclization (XI→XII) in a manner analogous to that used by Galinovsky and Nesvadba (1954). In the light of the preceding discussion of quaternary lupinine salts, any attempt to prepare a cyclic compound which commences with quaternization must fail, since the product would be the *cis*-compound analogous to VIIIb and would carry an equatorial hydroxymethyl group. The failure of Fodor, Sallay, and Dutka to achieve such a cyclization thus offers further support for the structure VIIIb. However, the nature of

the three compounds produced is not clear. Attempts to prepare the compound A in these laboratories were not successful. The crystalline product obtained had m.p. 160–162 °C after recrystallization and $[\alpha]_D^{20}$ +11·1° (*c*, 1·5 in water) essentially unaltered by heating in water at 95 °C for 16 hr. This rotation is in accord with expectations for the quaternary salt analogous to VIIIb, and this compound presumably corresponds to the compound C isolated by Fodor, Sallay, and Dutka.





(XI) (XII)

III. Hofmann Degradation of the Methiodides

Initially, experiments were confined to attempted racemization of the methiodides by the method used for cryptopleurine methiodide, but as this resulted only in recovery of unchanged material of unaltered rotation, more vigorous methods were used. Each methiodide was distilled with aqueous alkali, allowing the mixture to concentrate until the steam-volatile methine bases were detected in the distillate.* The reaction volume was then maintained at the critical level until about 50 per cent. conversion to methine bases was achieved, and the residual quaternary salt then recovered. In neither case was the recovered methiodide altered in its optical properties, indicating that

* This did not occur until the quaternary hydroxide actually separated out of the mixture; solution by addition of a little water immediately stopped the Hofmann elimination. Lupinine methohydroxide separated as a crystalline solid; no methine bases were detected until this became oily on continued concentration.

racemization cannot be achieved in this way. In other experiments, the reaction mixture was refluxed at its critical volume in order to allow the methines to recyclize if possible. The results were the same as in the distillation experiments. The methine bases accumulated in the reaction flask, indicating that their constant removal is not necessary for the Hofmann degradation to proceed. As a final check the methine bases were allowed to stand for several days (with periodic refluxing) in water, dilute alkali, and dilute acid (slight excess). In no case were any quaternary derivatives obtained.

From these results it seems clear that racemization at C_9 cannot be achieved under normal Hofmann conditions in the saturated quinolizidine nucleus.

IV. Experimental

All melting points are corrected. Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, at the University of Melbourne, under the direction of Dr. K. W. Zimmermann.

(a) *Reaction of (—)-Lupinine with Ethyl Iodoacetate*

(—)-Lupinine (0·20 g) in benzene (10 c.c.) was treated at room temperature (20–25 °C) with redistilled ethyl iodoacetate (0·50 g; approximately 2 m-equiv.). After 48 hr the benzene was decanted from the gum which had deposited and this was triturated with acetone. It failed to solidify so was dissolved by boiling and allowed to cool, when a crystalline solid was obtained. After recrystallization from acetone this was obtained as colourless needles, m.p. 160–161 °C (Found: C, 44·3; H, 6·9; I, 32·8%. Calculated for $C_{10}H_{19}ON.C_4H_7O_2I$: C, 43·8; H, 6·8; I, 33·1%) and had $[\alpha]_D^{20}$ +11·1° (*c*, 1·01 in H_2O) which was changed to +11·9° on heating for 24 hr at 100 °C. (The same solution was used in a sealed tube to prevent evaporation.)

(b) *Reaction of Lupinine Methiodides with Alkali*

(i) (+)-*epi*Lupinine methiodide (6·0 g, m.p. 252–253 °C; $[\alpha]_D^{20}$ +5·6° (*c*, 2·6 in H_2O)) in water (120 c.c.) containing potassium hydroxide (38 g) was distilled, maintaining the volume approximately constant by dropwise addition of water. No volatile bases were detected in the acidified distillate (Mayer's reagent), so the solution was allowed to concentrate. A heavy oil began to separate after reduction to approximately half volume ([KOH]~60% w/v) and volatile base was detected in the distillate. This ceased on dilution of the reaction mixture with water (which caused the oil to redissolve) and reappeared on concentration. After 3 hr distillation under these conditions (volume constant at c. 60 c.c.) 1·32 g methine base mixture was extracted from the distillate, and 0·01 g from the reaction mixture with ether. The reaction mixture was then refluxed (1 hr), affording a further 0·62 g tertiary base in the mixture, thus indicating that removal by distillation was not necessary for the reaction to proceed. The alkaline solution was then treated with the calculated amount of perchloric acid, cooled, filtered, and evaporated to dryness. The residue was freed from potassium perchlorate by extraction with boiling ethanol, and the extract concentrated to crystallization. The methiodide (1·37 g) was recovered as colourless prisms, m.p. 252–253 °C (Found: C, 42·6; H, 7·1; I, 40·6%. Calc. for $C_{10}H_{19}ON.CH_3I$: C, 42·5; H, 7·1; I, 40·8%), undepressed by admixture with the starting material, and had $[\alpha]_D^{20}$ +4·7° (*c*, 5·4 in H_2O). The total recovery was 83% (60% as methine bases, 23% as methiodide).

(ii) (—)-Lupinine methiodide (3·5 g, m.p. 295 °C (decomp.); $[\alpha]_D^{20}$ +10·5° (*c*, 5·5 in H_2O)) was treated as described above, with similar results. The quaternary hydroxide separated as a crystalline solid on concentration to 50 c.c. ([KOH]~40% w/v) but methine bases did not appear in the distillate till this became oily on continued concentration ([KOH]~50% w/v). The methine bases (1·62 g, 86%) and methiodide (0·15 g, 4·5%) were recovered as described above. The methiodide had m.p. 295 °C (decomp.) (Found: C, 42·4; H, 7·0; I, 40·6%. Calc. for $C_{10}H_{19}ON.CH_3I$: C, 42·5; H, 7·1; I, 40·8%), undepressed by admixture with the starting material, and had $[\alpha]_D^{20}$ +12·5° (*c*, 0·5 in H_2O). Total recovery was 90%.

V. Acknowledgment

The author is indebted to Professor M. Carmack of Indiana University, U.S.A., for the (−)-lupinine used in this investigation.

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THE CONSTITUENTS OF THE KINO OF *EUCALYPTUS MACULATA* HOOK.

By R. J. Gell,* J. T. Pinhey,* and E. Ritchie*

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Summary

Ellagic acid, *p*-hydroxycinnamic acid, naringenin, and a new flavanolone, aromadendrin 7-methyl ether, have been isolated from the kino of *Eucalyptus maculata* Hook.

I. Introduction

Although the exudation of kinos following injury to their barks is a conspicuous feature of many species of *Eucalyptus*, and indeed is presumably the origin of the vernacular name, "gum tree", little is known of the structures of their chemical constituents. Early work has been summarized by Hillis (1951, 1952), who examined several kinos by chromatographic techniques (1951), isolated aromadendrin, kaempferol, and ellagic acid from *E. calophylla* R.Br. and aromadendrin and ellagic acid from *E. corymbosa* Sm.; and showed that aromadendrin was 3,4′,5,7-tetrahydroxyflavanone (1952).

Smith (1913) stated that the kino of *E. maculata* Hook. contained aromadendrin but gave no details of its isolation. Later, Ware (1925) on the basis of colour tests arrived at the same conclusion. In the present investigation four samples of kino were examined and each subjected to the same isolation procedure. Two samples, designated A and B, were obtained from trees which had been sprayed with a herbicide containing butyl-2,4,5-trichlorophenoxyacetic acid in the course of forestry clearing operations but the other two, C and D, were from untreated trees.

Aromadendrin could not be isolated from any of the samples but all yielded a new flavanolone, which analysed for $C_{16}H_{14}O_6$ and contained one methoxyl group. On aerial oxidation in alkaline solution it yielded the known 7-methyl ether of kaempferol and hence was the 7-methyl ether of aromadendrin. The crude flavanolone was always coloured bright yellow by the kaempferol derivative and in a preliminary experiment the pigment could be readily isolated from a crude flavanolone fraction which had been kept in solution in dilute sodium hydroxide for some time. In later experiments no attempt was made to isolate it, since it is probable that most, if not all of it, was an artefact.

From samples A, B, and D, *p*-hydroxycinnamic acid was isolated, but not from sample C. However, the latter gave a substantial amount of naringenin which could not be obtained from the other samples.

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Ellagic acid was isolated from all samples, although in variable amounts. This substance has recently been shown to be quite ubiquitous in the plant kingdom (Bate-Smith 1956).

In Table 1 the yields of the substances isolated from the four samples are given.

Before the constituents of D had been isolated it was an attractive hypothesis that the herbicide had stopped the synthesis of naringenin at the stage of *p*-hydroxycinnamic acid, which may be regarded as a precursor or at least as a structural unit of naringenin, but now such a simple hypothesis is not tenable. The variability observed in the kino constituents is possibly more readily explained by atmospheric weathering and/or natural variation.

TABLE 1
YIELDS OF FLAVONOIDS AND ACIDS

Yields (%)	Samples			
	A	B	C	D
Aromadendrin 7-methyl ether ..	0·8	1·7	0·8	0·3
Naringenin	0	0	0·2	0
p-Hydroxycinnamic acid	0·6	0·015	0	0·05
Ellagic acid	0·3	0·5	0·3	0·1

II. EXPERIMENTAL

Melting points are uncorrected. The analyses were carried out by Dr. K. W. Zimmermann of the C.S.I.R.O. Microanalytical Laboratory at the University of Melbourne, and by Miss B. Stevenson, University of Sydney. Light petroleum refers to the fraction b.p. 60–90 °C.

(*a*) *Extraction of the Kino.*—The kino (350 g) was dissolved in warm methanol (1000 ml), the solution filtered from fragments of bark, and concentrated to rather less than half of its bulk. The dark viscous residue, whilst still warm, was diluted with ether (1000 ml), the mixture shaken thoroughly, and kept overnight. The lower layer (L) was separated from the ether layer which was washed several times with water and then extracted successively with saturated sodium bicarbonate (3 × 100 ml), 1N sodium carbonate (3 × 100 ml), and 3N sodium hydroxide (3 × 100 ml). The several extracts were acidified, shaken with ether, and the ethereal solutions, after drying, evaporated to yield the crude fractions. The original ether extract yielded only a trace of brownish yellow oil.

(*b*) *Ellagic Acid.*—From sample B crude ellagic acid separated as a brown amorphous solid when the original ether extract was shaken with water and with the aqueous sodium bicarbonate. In the other samples it remained in the layer L. This was freed from methanol, the residue dissolved in acetone, and the solution passed through a large column of alumina which had been prepared in acetone containing 5% glacial acetic acid. The eluates were evaporated and the dark viscous residue stirred with ethyl acetate when a brown amorphous solid separated. It was collected, washed thoroughly with ethyl acetate, and then with a little methanol. The crude material could be crystallized from pyridine when it separated as brownish yellow needles, m.p. above 360 °C, but satisfactory analyses could not be obtained until it was regenerated from its purified acetyl derivative.

The acetyl derivative prepared by refluxing the acid (0·5 g) with anhydrous sodium acetate (0·5 g) and acetic anhydride (20 ml) for 4 hr, crystallized from acetic anhydride in colourless needles, m.p. 340 °C (depending on rate of heating) (Found: C, 56·0; H, 3·1%. Calc. for $C_{22}H_{14}O_{12}$: C, 56·2; H, 3·0%). Perkin and Nierenstein (1905) record m.p. 343–346 °C.

The acetyl derivative (0·3 g) was hydrolysed by refluxing with acetic acid (5 ml) and sulphuric acid (0·5 ml) for 2 hr. The mixture was diluted with water and the crystalline precipitate collected. The acid crystallized from pyridine in cream coloured needles, m.p. above 360 °C (Found: C, 55·2; H, 2·2%. Calc. for $C_{14}H_{16}O_8$: C, 55·6; H, 2·0%). It gave a blue ferric test and a cherry-red colour with concentrated nitric acid.

(c) p-*Hydroxycinnamic Acid.*—The fraction extracted by sodium bicarbonate, which formed a reddish brown gum, was chromatographed in ethereal solution on an alumina column prepared in ether containing 5% glacial acetic acid. The eluates on evaporation afforded a pale yellow gummy solid which crystallized from water in colourless needles, m.p. 212–214 °C (decomp.), undepressed by authentic *p*-hydroxycinnamic acid (Found: C, 65·8; H, 5·2%. Calc. for $C_9H_8O_3$: C, 65·8; H, 4·9%).

The acetyl derivative prepared by the action of acetic anhydride in the presence of perchloric acid, crystallized from ethyl acetate-light petroleum in colourless needles, m.p. 205–207 °C, undepressed by authentic *p*-acetoxycinnamic acid (Found: C, 64·3; H, 5·0%. Calc. for $C_{11}H_{10}O_4$: C, 64·1; H, 4·9%).

(d) *Naringenin.*—The sodium carbonate soluble fraction of sample C on purification by chromatography as in (c) above, gave a solid which crystallized from aqueous ethanol in colourless needles, m.p. 250–251 °C, undepressed by authentic naringenin (Found: C, 66·2; H, 4·7; O, 29·1%. Calc. for $C_{15}H_{12}O_5$: C, 66·2; H, 4·4; O, 29·4%). On degradation with boiling 30% potassium hydroxide there was obtained *p*-hydroxycinnamic acid and after fusion with potassium hydroxide at 220 °C, phloroglucinol was detected by paper chromatography.

The corresponding fractions from samples A and D were small amounts of reddish brown gums from which no crystalline substance could be isolated, but the fraction from sample B, although containing no naringenin as shown by paper chromatography, consisted essentially of the flavanolone.

(e) *Aromadendrin 7-Methyl Ether.*—The sodium hydroxide soluble fractions of each of the samples and the sodium carbonate soluble fraction of sample B were chromatographed as in (c) above. On evaporation, the eluates gave a bright yellow gummy solid which after several recrystallizations from aqueous ethanol afforded colourless needles, $[\alpha]_D^{22°}$ +21° (*c*, 0·95 in ethanol). On heating in a soda glass capillary they fused at about 193 °C, depending on the rate of heating, to an orange-yellow melt, indicating that some conversion to the flavonol was occurring (cf. Hillis 1952) (Found: C, 63·5; H, 4·8; O, 31·4; OCH_3, 9·9%. Calc. for $C_{16}H_{14}O_6$: C, 63·5; H, 4·6; O, 31·8; $1 \times OCH_3$, 10·3%). It gave a port wine coloured ferric test.

(f) *Kaempferol 7-Methyl Ether.*—Air was bubbled through a solution of the flavanolone (1 g) in 8% sodium hydroxide for 4 hr. After acidification, the reaction mixture was extracted with ether and the dried extract passed through a column of acetic acid-washed alumina in the usual manner. The product crystallized from ethanol in yellow needles, m.p. 224–225 °C, undepressed by an authentic specimen of kaempferol 7-methyl ether (Found: C, 62·2; H, 4·3%. Calc. for $C_{16}H_{12}O_6.\frac{1}{2}H_2O$: C, 62·1; H, 4·2%). Hillis (1952), who prepared the substance by alkylation of aromadendrin, also obtained it in this hydrated form.

The triacetyl derivative prepared by the action of acetic anhydride in the presence of perchloric acid crystallized from ethanol-light petroleum in colourless needles, m.p. 201 °C (lit. 201 °C) (Found: C, 61·8; H, 4·2%. Calc. for $C_{22}H_{18}O_9$: C, 62·0; H, 4·2%).

III. Acknowledgments

The authors are indebted to Mr. W. E. Hillis, Division of Forest Products, C.S.I.R.O., for helpful advice and for providing a sample of kaempferol 7-methyl ether, to Mr. P. Martin and Mr. L. Bryant of the Forestry Commission of New

South Wales for supplies of kino and results of some preliminary work on the separation of the constituents, and to General Motors-Holden's Ltd. for the award of a scholarship to one of them (J.T.P.).

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CONSTITUENTS OF *MELICOPE SARCOCOCCA* LAUT.

By T. A. GEISSMAN*

[*Manuscript received February* 25, 1958]

Summary

Among the constituents of the bark of *Melicope sarcococca* Laut. (Rutaceae) have been found two optically active flavanones: (—)-4′,5-dihydroxy-3′,7-dimethoxyflavanone, and its 4′-prenyl ether. The occurrence of the flavanone prenyl ester is of interest in view of the occurrence of coumarin and furocoumarin isoprenoid ethers in the family Rutaceae.

I. INTRODUCTION

Examination of the bark of *Melicope sarcococca* Laut., a rutaceous tree indigenous to New Guinea, has led to the isolation of two crystalline, non-alkaloidal substances. These were recognized to be flavanones by their colour

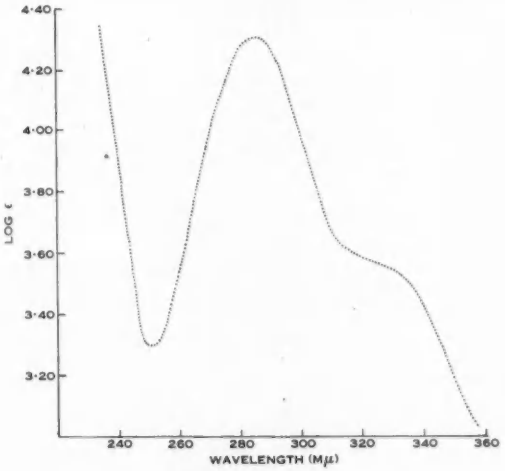

Fig. 1.—Absorption spectrum of flavanone I in ethanol.

reactions and by the ultraviolet absorption spectrum (Fig. 1) of one of them. These compounds have been shown to have the structures I and II, and are of particular interest for two reasons: they are both optically active, and one of them possesses the unusual structural feature of an ether-linked *iso*pentenyl

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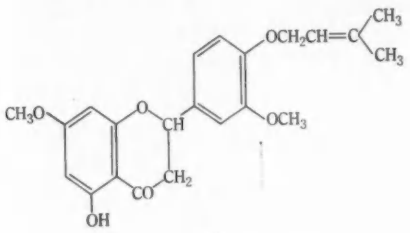
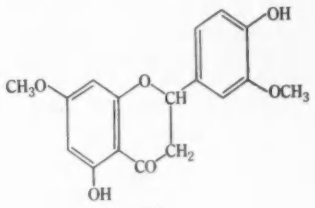
(prenyl) residue. It is possible that flavanone II is not present in the plant, and arose by deprenylation of flavanone I in the isolation procedure.

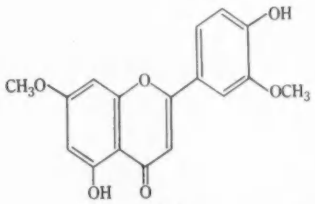
Flavanone I readily lost the fragment $-C_5H_8$ when it was treated with a trace of mineral acid in hot acetic acid solution, and yielded a new flavanone III isomeric with flavanone II. The optical activity of I and II, and the lack of activity in III, indicated that the formation of III by removal of an ether-linked side chain in I was accompanied by racemization. That I is indeed the



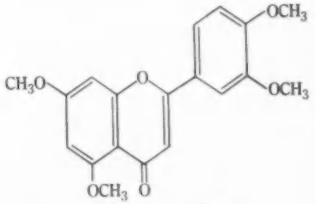
(I)



(II)

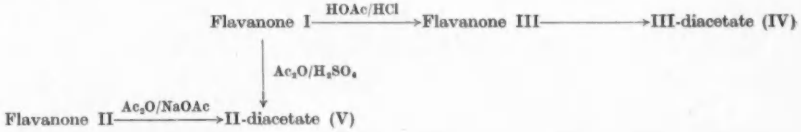


(VI)



(VII)

prenyl derivative of II is shown by the conversion of I and II, without racemization, into the same diacetate (V), formed from I by acetylation under acidic conditions that effected removal of the prenyl residue, and from II by acetylation under the usual conditions with sodium acetate as the catalyst.



The hydroxylation pattern of I and II was shown by their dehydrogenation to a flavone (VI), and methylation of the latter to luteolin tetramethyl ether (VII).* That both I and II have a methoxyl, and not a hydroxyl, group in the

* The ultraviolet absorption spectrum of luteolin tetramethyl ether has not been recorded in the literature, and so it is given here (Fig. 3).

7-position is shown by the purple colour that both give with concentrated nitric acid (Rao and Seshadri 1949).* The presence of a free 5-hydroxyl group in VI (and thus in II) was clearly shown by the shift in the absorption spectrum of flavone VI in the presence of aluminium chloride (Fig. 2). Indeed, the spectra of VI in ethanol and in ethanol in the presence of aluminium chloride show a striking resemblance to those of luteolin itself (Jurd and Geissman 1956). Flavanone II is therefore either 4′,5-dihydroxy-3′,7-dimethoxy flavanone, or 3′,5-dihydroxy-4′,7-dimethoxy flavanone. That it is the first of these was shown by the preparation of the latter from hesperetin, and the dehydrogenation of this to the corresponding 3′,5-dihydroxy-4′,7-dimethoxyflavone. The synthetic compounds were not identical with flavanone III and its related flavone, and thus the natural compound is the 4′,5-dihydroxy-3′,7-dimethoxy isomer.

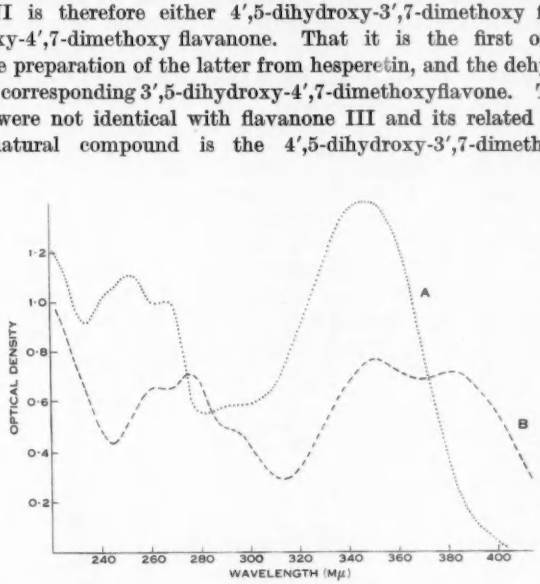


Fig. 2.—Absorption spectra of flavone VI. *A*, in ethanol ($6{\cdot}37 \times 10^{-5}$M); *B*, in ethanol containing 2 per cent. aluminium chloride.

Additional evidence for this structure is that flavanones I and II give a brown ferric chloride colour (thus, the two hydroxyl groups are not 3′,4′-), and no veratric acid could be isolated when flavanone I was oxidized with permanganate (thus, the two methoxyl groups are not 3′,4′-).

The nature and location of the C_5H_8-residue in flavanone I are shown by the following observations. Chromic acid oxidation of the flavanone yielded acetone, isolated and identified as the 2,4-dinitrophenylhydrazone. The presence of a carbon-linked methyl group was shown by analysis, and the flavanone readily absorbed bromine (in chloroform solution) without evolution of HBr. These observations, coupled with the ready removal of the C_5H_8-residue under mild conditions, show that this grouping is an ether-linked 1-(3-methyl-2-butenyl) group.

* 5-Hydroxy-7-methoxyflavanones give green to blue colours with HNO_2; 5,7-dihydroxyflavanones do not.

The prenyl group can only be found attached at the 5- or 4′-position. That it is in the latter is indicated by the purplish brown ferric chloride colour of the flavanone, a colour characteristic of 5-hydroxyflavan-4-ones ; and by the near-insolubility of flavanone I in aqueous alkali. Flavanone II, having a free 4′-hydroxyl group, is instantly soluble in dilute aqueous sodium hydroxide.

While the occurrence of ethers containing isoprenoid alkyl residues is common among the naturally occurring coumarins (Dean 1952) found chiefly in umbelliferous and rutaceous plants, compounds of this type have not heretofore been encountered among the flavonoid constituents of these plants. The presence of an isoprenoid residue as a nuclear substituent in phellamurin and amurensin (Hasegawa and Shirato 1953) is of interest in this connection since *Phellodendron amurense*, from which these 8-(3-hydroxy-3-methylbutyl) flavanoids are isolated, is also a member of the family Rutaceae.

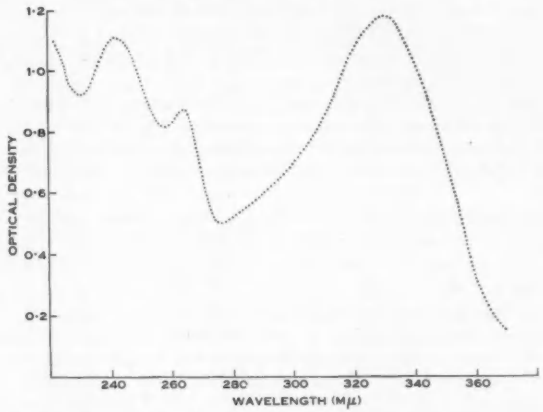


Fig. 3.—Absorption spectrum of luteolin tetramethyl ether in ethanol ($4 \cdot 68 \times 10^{-5}$M).

II. Experimental

The bark was collected by Dr. R. D. Hoogland, who identified the tree as *Melicope sarcococca* Laut.*

(i) *Extraction.*—570 g of the dried and milled bark was exhaustively extracted with (i) light petroleum (40–60 °C), and (ii) methanol. The extracted bark sample weighed 315 g.

The light petroleum extract on standing deposited a tarry, semicrystalline substance. This was rubbed with methanol, when it formed a white, crystalline material. After washing with fresh methanol the crude material weighed 15·3 g. After recrystallization from glacial acetic acid-water (3 : 1), a yield of 11·0 g of flavanone I, (—)-3′,7-dimethoxy-5-hydroxy-4′-[1-(3-methyl-2-butenoxy)]flavanone, was obtained. This material (m.p. 146–147 °C) contained solvent, for after recrystallization from ethyl acetate-methanol it formed soft, white needles, m.p. 165–166 °C (Found : C, 68·9 ; H, 6·4 ; OCH_3, 16·1 ; *C*-CH_3, 3·2%. Calc. for $C_{22}H_{24}O_6$: C, 68·7 ; H, 6·3 ; $2 \times OCH_3$, 16·1 ; $1 \times C$-CH_3, 3·9%) ; $[\alpha]_D^{20}$ —34·1° (*c*, 3·6 in $CHCl_3$).

* The identification is preliminary, and is to be referred to the collector's number : " Hoogland and Pullen 6140 ".

The flavanone (I) was nearly insoluble in aqueous 2N sodium hydroxide, but dissolved in methanolic sodium hydroxide to form a pale yellow solution, darkening to orange on heating or standing. It gave a deep red-orange colour with concentrated sulphuric acid, a purplish brown colour with ferric chloride (in ethanol), a deep red-purple colour with magnesium-concentrated hydrochloric acid (in ethanol), and a purplish blue colour with concentrated nitric acid. A solution of the flavanone in chloroform instantly absorbed bromine (added in carbon tetrachloride solution).

(ii) *Monoacetate of I.*—Treatment of the flavanone (I) with sodium acetate-acetic anhydride refluxing for about 1 min gave the *monoacetate*, white needles from dilute acetic acid, m.p. 182–183 °C (Found: C, 67·5; H, 6·1; OAc, 10·2%. Calc. for $C_{24}H_{26}O_7$: C, 67·6; H, 6·1; OAc, 10·1%).

(iii) *4′-Acetoxy-5-hydroxy-3′,7-dimethoxyflavanone.*—A suspension of 440 mg of flavanone I in 4 ml of acetic anhydride containing 6 drops of concentrated sulphuric acid was kept at 0 °C until a clear solution was obtained. Ice was added and after the initial vigorous decomposition was complete, water and ether were added, the ether layer washed with aqueous sodium bicarbonate and water, dried, and evaporated. The residual oil crystallized on rubbing with methanol. Recrystallized from acetone-methanol, the compound formed tiny white prisms, m.p. 130–131 °C. It gave a deep red-brown ferric chloride colour (in ethanol) (Found: C, 63·9; H, 5·1; OAc, 12·5; OCH_3, 16·9%. Calc. for a monoacetate of $C_{17}H_{16}O_6$ ($C_{19}H_{18}O_7$): C, 63·7; N, 5·1; 1×OAc, 12·0; 2×OCH_3, 17·3%).

(iv) *4′,5-Diacetoxy-3′,7-dimethoxyflavanone.*—A sample of 300 mg of flavanone I was acetylated with acetic anhydride-sulphuric acid, and the product acetylated further by treatment with acetic anhydride-sodium acetate. After decomposition of the acetic anhydride the crystalline product was recrystallized from acetone-methanol, from which it formed tiny white prisms, m.p. 148–149 °C.

In another acetylation experiment with acetic anhydride-sulphuric acid, in which the decomposition of the reaction mixture was carefully controlled by cooling, the same compound was obtained without the necessity for reacetylation (Found: OAc, 21·2; O, 32·2%. Calc. for a diacetate of $C_{17}H_{16}O_6$ ($C_{21}H_{20}O_8$): 2×OAc, 21·5; O, 32·0%).

(v) (±)-*4′,5-Dihydroxy-3′,7-dimethoxyflavanone* (*III*).—A solution of 1·0 g of flavanone I in 15 ml of glacial acetic acid containing 1 ml of concentrated hydrochloric acid was heated for 1 hr in a boiling water-bath. The cooled solution was poured into ether and water and the ether layer washed with aqueous sodium bicarbonate and water, and dried over sodium sulphate. Removal of the ether left a crystalline residue (0·88 g) which crystallized from methanol-water as shining leaflets, m.p. 147–148 °C (Found: C, 64·3; H, 5·3; OCH_3, 20·0%. Calc. for $C_{17}H_{16}O_6$: C, 64·5; H, 5·1; 2×OCH_3, 19·7%); $[\alpha]_D^{20}$ 0·00° (*c*, 3·12 in $CHCl_3$).

The compound gave a red-purple colour with magnesium-hydrochloric acid, and a deep purplish blue colour with concentrated nitric acid.

(vi) (±)-*4′,5-Diacetoxy-3′,7-dimethoxyflavanone.*—Acetylation of the racemic flavanone with acetic anhydride-sodium acetate gave the *diacetate*, colourless prisms from methanol, m.p. 159–160 °C (Found: C, 63·2; H, 5·2; OAc, 20·0; OCH_3, 16·0%. Calc. for $C_{21}H_{20}O_8$: C, 63·0; H, 5·0; 2×OAc, 21·5; 2×OMe, 15·5%).

(vii) *Flavanone II* ((—)-*4′,5-Dihydroxy-3′,7-dimethoxyflavanone*).—The aqueous acetic acid mother liquor (from the recrystallization of the crude flavanone obtained from the light petroleum extract of the bark) was diluted with much water, and the precipitate washed with cold methanol. The residue (1·4 g) was recrystallized from acetone-methanol, from which it was obtained as tiny, white needles, m.p. 167–168 °C. A mixture of flavanone I (m.p. 165–166 °C) and flavanone II (m.p. 167–168 °C) melted at about 145–150 °C (Found: C, 64·8; H, 5·2; OCH_3, 19·7%. Calc. for $C_{17}H_{16}O_6$: C, 64·5; H, 5·1; 2×OCH_3, 19·7%); $[\alpha]_D^{20}$ —32·2° (*c*, 1·8 in $CHCl_3$).

Flavanone II, in contrast to flavanone I, was instantly soluble in cold, dilute aqueous sodium hydroxide. It gave a brown colour with ferric chloride (ethanol), a deep brownish purple colour with concentrated nitric acid, and an intense purple-red colour with magnesium-hydrochloric acid.

(viii) *Diacetate of Flavanone II.*—Acetylation of flavanone II with acetic anhydride-sodium acetate gave the *diacetate*, m.p. 148–149 °C (from acetone-methanol) (Found: C, 63·0; H, 5·1; OAc, 22·5; OCH_3, 15·6%. Calc. for diacetate of $C_{17}H_{16}O_6$ ($C_{21}H_{20}O_8$): C, 63·0; H, 5·0; 2×OAc, 21·5; 2×OCH_3, 15·5%).

A mixture of the diacetate of flavanone II (m.p. 148–149 °C) and the diacetate prepared from flavanone I by means of acetic anhydride-sulphuric acid (m.p. 148–149 °C) melted at 148–149 °C.

(ix) *Alkaline Degradation of Flavanone I.*—To a fused mixture of 5 g of potassium hydroxide and 1 ml of water at 190 °C was added 500 mg of flavanone I. After 10 min at 190–220 °C the mixture was cooled, dissolved in water, acidified, and extracted with ether. The sodium bicarbonate extract of the ether solution was acidified, extracted with ether, and the ether solution dried, treated with charcoal, and evaporated. The oily residue crystallized on rubbing; recrystallized from benzene, it melted at 194–196 °C, and when mixed with protocatechuic acid, m.p. 198–199 °C, the m.p. was 197–198 °C. The compound gave a deep green colour with ferric chloride.

Acetylation of the acid, m.p. 194–196 °C, gave 3,4-diacetoxybenzoic acid, m.p. 155–156 °C (Herzig (1885) reports 151–153 °C) (Found: C, 55·5; H, 4·5%. Calc. for $C_{11}H_{10}O_6$: C, 55·5; H, 4·3%).

(x) *Oxidation of Methylated Flavanone I.*—Methylation of flavanone I, first with methyl sulphate and potassium carbonate in acetone and then, after treatment with acetic acid-hydrochloric acid, with methyl sulphate and methanolic alkali yielded an orange oil that could not be induced to crystallize. It was dissolved in acetone and treated with powdered potassium permanganate until the colour was permanent. The mixture was filtered and the solid dissolved in a solution of sodium bisulphite-sulphuric acid. Extraction with ether afforded a solid which crystallized from water as colourless needles, m.p. 179–180 °C. A mixture of this material with authentic veratric acid (m.p. 179–180 °C) melted at 179–180 °C.

(xi) *3′,5-Dihydroxy-4′,7-dimethoxyflavanone and 3′,5-Dihydroxy-4′,7-dimethoxyflavone.*—These products were prepared from hesperetin according to Gupta, Narasimhachari, and Seshadri (1953). The flavanone (reported m.p. 161–162 °C) had m.p. 161–162 °C (mixed with flavanone II, m.p. 167–168 °C, the m.p. was below 140 °C), and the flavone had m.p. 228–229 °C (reported 225–226 °C). The higher m.p. of the flavone than that previously reported probably indicates a somewhat higher degree of purity; the magnesium-hydrochloric acid colour was a bright red-orange, while the Indian workers report the colour as red-brown. The *diacetate* of the flavone was prepared; it had m.p. 182–183 °C (reported m.p. 182 °C).

(xii) *Dehydrogenation of Flavanone II: 4′,5-Dihydroxy-3′,7-dimethoxyflavone (VI).* — A solution of 500 mg of flavanone II and 2 g of fused potassium acetate in 10 ml of glacial acetic acid was heated to boiling and a solution of 500 mg of iodine in 10 ml of glacial acetic acid was added in portions over 45 min. The resulting solution was refluxed for an additional 30 min, cooled, and poured into a solution of sodium metabisulphite in ice water. Ether was added and the insoluble material collected by filtration. Evaporation of the ether layer gave an additional amount of product (total 260 mg).

Recrystallized from ethyl acetate-methanol, the flavone formed tan leaflets, m.p. 223–224 °C. It gave a red-orange colour with magnesium-hydrochloric acid (Found: C, 63·2; H, 4·9; OCH_3, 19·5%; Found (after drying 150 °C/P_2O_5): C, 64·2; H, 4·5%. Calc. for $C_{17}H_{14}O_6$: C, 65·0; H, 4·5; 2×OCH_3, 19·7%. Calc. for $C_{17}H_{14}O_6 \cdot \frac{1}{2}H_2O$: C, 63·2; H, 4·7; 2×$OCH_3$, 19·2%).*

The *diacetate* of the flavone, prepared in the usual way, formed tiny white needles from acetone-methanol, m.p. 206–207 °C.

Dehydrogenation of flavanone I under the same conditions led to the same flavone, m.p. 223–224 °C.

* Gupta, Narasimhachari, and Seshadri (1953) found that 3′,5-dihydroxy-4′,7-dimethoxyflavone also gave analytical values in agreement with $C_{17}H_{14}O_6 \cdot \frac{1}{2}H_2O$.

(xiii) *Methylation of 4′,5-Dihydroxy-3′,7-dimethoxyflavone (VI) to Luteolin Tetramethyl Ether.*—To a solution of 210 mg of the flavone, m.p. 223–224 °C, from flavanone II, in 15 ml of ethyl acetate was added an ether solution of diazomethane prepared from 6 g of nitrosomethylurea. After the addition of 40 ml of methanol, the solution was kept overnight, then treated with acetic acid to destroy the excess diazomethane. The solution was washed with water and evaporated to dryness. The crystalline residue was removed, washed with methanol, and recrystallized from ethyl acetate-light petroleum (40–60 °C) as soft buff needles, m.p. 191–192 °C. A mixed m.p. with authentic luteolin tetramethyl ether, m.p. 189–190 °C, prepared by diazomethane methylation of diosmetin, was undepressed, m.p. 189–190 °C (Found : C, 66·6 ; H, 5·5%. Calc. for $C_{19}H_{18}O_6$: C, 66·6 ; H, 5·3%).

(xiv) *Oxidation of Flavanone I.*—A solution of 0·65 g of flavanone I in 10 ml of glacial acetic acid was treated with 0·4 g of chromium trioxide dissolved in 4 ml of 50 per cent. aqueous acetic acid. After 3 days the mixture was diluted with water, neutralized with sodium hydroxide, and distilled. The 25 ml of distillate was redistilled, 5 ml being collected, to which a saturated solution of 2,4-dinitrophenylhydrazone in 2N aqueous hydrochloric acid caused the formation of a copious precipitate. This was collected and recrystallized from ethanol, from which it formed orange-yellow needles melting at 125–126 °C ; m.p. was unchanged on admixture with authentic acetone 2,4-dinitrophenylhydrazone.

(xv) *Absorption Spectra.*—These were determined in ethanol solution, using a Unicam ultra-violet spectrophotometer.

III. Acknowledgments

The author wishes to express his gratitude to Dr. J. R. Price for making available the material used in this work and for his helpful interest in the progress of the study. To the Educational Foundation, U.S.A., he is grateful for the award of a Fulbright Senior Scholarship for 1957–58, and to the C.S.I.R.O. for the hospitality of the laboratories of the Division of Industrial Chemistry.

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SHORT COMMUNICATIONS

POLAROGRAPHIC RESIDUAL CURRENT–TIME CURVES*

By H. A. McKenzie†

The author has made a study of polarographic diffusion current-time curves and the Ilkovic equation (McKenzie 1958). In the course of this work a number of pertinent observations were made on residual current-time curves. They are briefly presented in this paper.

Polarographic residual currents (i_r) may be considered to be made up of two parts: a charging current (i_c) and a faradic current (i_f). The charging current is assumed to result from the orientation of charges in the electrical "double" layer at the surface of the emerging mercury drop resulting in its behaviour as a capacitor of increasing surface area. The instantaneous charging current is given by (see Loveland and Elving (1952), who obtain a slightly different value for the numerical constant)

$$i_c = 0{\cdot}00567 k m^{\frac{1}{3}} \tau^{-\frac{1}{3}} \Delta E, \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where k is the capacity constant, ΔE the potential difference between the electrocapillary maximum and the applied voltage, m is the rate of flow of mercury in mg sec^{-1}, and τ the time in sec.

The faradic component forms mainly from traces of mercury ions and oxygen remaining in the solution after deaeration.

Very few attempts have been made to verify this simple treatment of residual current experimentally. Lingane and Loveridge (1944) found that the *average* residual current determined experimentally for different capillaries could be treated as the sum of capacity and faradic currents. Later Taylor, Smith, and Cooter (1949) assumed that the residual current was solely a charging current and examined their oscillographic data accordingly. Their treatment was not successful. This is not surprising as an examination of their data indicates that there was an appreciable faradic component contributing to the total observed current. Recently Bresle (1956) has examined instantaneous residual current-time curves during the later stages of drop life for 0·1M potassium chloride (0·09 per cent. gelatin) on the negative branch of the electrocapillary curve. He found his curves to be in accord with the above treatment (i.e. involving i_c and i_f).

The present author has examined residual current-time curves for 0·1M potassium chloride, both in the presence and absence of gelatin (0·01g/100 ml) on the positive and negative branches of the electrocapillary curve, at 25 °C.

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A Brush oscillograph with modified input was used for recording the curves. This enabled measurements to be made from 0·35 sec (approximately) to the end of the drop time (*c.* 4 sec). Some measurements (from 1 sec approx. to the end of drop) were also made with the recording polarograph described by McKenzie and Taylor (1958).

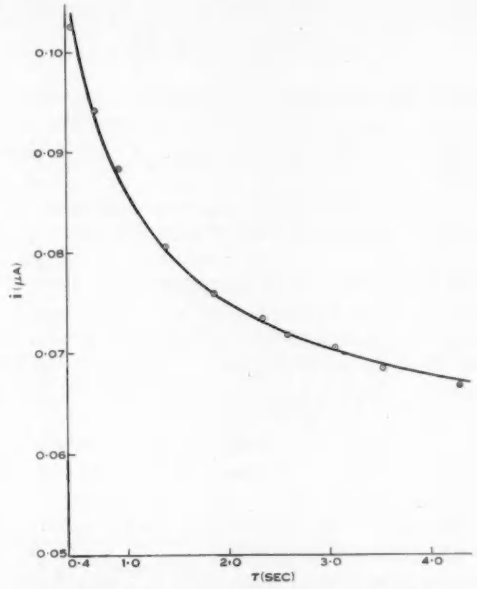

Fig. 1.—Residual current-time curve for 0·1M potassium chloride, no suppressor, at —0·76 V. Individual points are experimental data. The curve is for the fitted equation.

According to the above treatment,

$$i_r = i_c + i_f \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

$$= 0{\cdot}00567 k m^{\frac{2}{3}} \tau^{-\frac{1}{6}} \Delta E + i_f \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Considering the work of McKenzie (1958) and Taylor, Smith, and Cooter (1949) on diffusion current-time curves, the nature of i_c and i_f and the portion of the drop life being evaluated, it is adequate to represent $i_f = b\tau^{\frac{1}{2}}$, where b is a constant for the capillary and solution under consideration.

Thus

$$i_r = a\tau^{-\frac{1}{6}} + b\tau^{\frac{1}{2}}, \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

where

$$a = 0{\cdot}00567 k m^{\frac{2}{3}} \Delta E. \quad \ldots\ldots\ldots\ldots\ldots\ldots (5)$$

In Figure 1, typical residual current-time data for 0·1M potassium chloride, no suppressor, at —0·76 V (*v.* saturated calomel electrode) are shown. An attempt was made to fit equation (4) to the data by a least squares method (Coote, personal communication). The curve is plotted from the computed

equation. It is seen by inspection that it gives a satisfactory fit to the experimental data. The value obtained for a was 0·0680 (±0·0006) and for b was 0·0177 (±0·0005). The potential of the electrocapillary zero was found to be −0·47±0·02 V (*v.* saturated calomel electrode). The value obtained for m was 1·84 mg sec^{-1}. Substituting in equation (5), a value of 28±2 μF cm^{-2} was found for the capacity constant. Measurements were also made at −0·76 V for 0·1M potassium chloride containing gelatin (0·01 g/100 ml). A slightly less satisfactory fit was obtained for the data in the presence of gelatin. The value obtained for a was 0·0601 (±0·00097) and for b 0·0267 (±0·0008) from which a

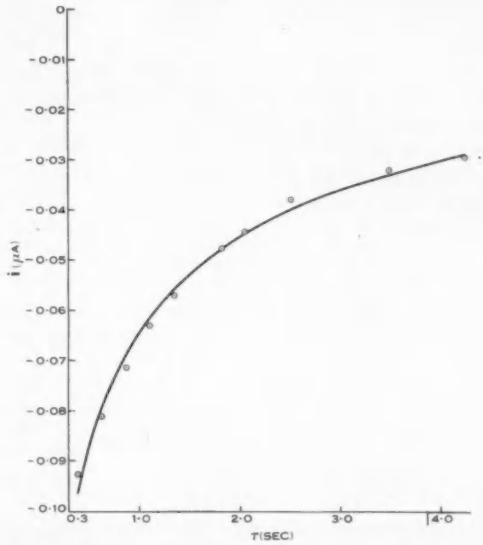

Fig. 2.—Residual current-time curve for 0·1M potassium chloride, no suppressor, at −0·22 V. Individual points are experimental data. The curve is for the fitted equation.

value of k of 24±2 μF cm^{-2} was calculated. Both of these values are in fair agreement with the values of the capacity constant reported from electrocapillarity studies by Philpot (1932) (22 μF cm^{-2}) and Grahame (1949) (19 μF cm^{-2}).

In Figure 2, residual current data are shown for 0·1M potassium chloride with no suppressor present, at −0·22 V. The curve shown appears to be a satisfactory fit to the experimental data. A value was obtained for a of −0·0781 (±0·0018) and for b of 0·0140 (±0·0015) from which k was computed to be 37±3 μF cm^{-2}, which is in satisfactory agreement with the value of 38 μF cm^{-2} obtained by Grahame (1949) from electrocapillarity studies. An attempt was made to fit equation (4) to data at −0·22 V for 0·1M potassium chloride containing gelatin. A less satisfactory fit was obtained as can be seen from Figure 3.

These and other experiments show that, in the absence of maximum suppressors, there is satisfactory agreement between the experimentally determined residual current and that computed assuming the current is made up of a capacity component and a faradic component. In the presence of gelatin, agreement with the theory was not as satisfactory, particularly on the positive branch of the electrocapillary zero. The surface active behaviour of gelatin is probably responsible for this. This is interesting in view of recent work on the effect of surface active agents on the polarized electrode (see Breyer 1956).

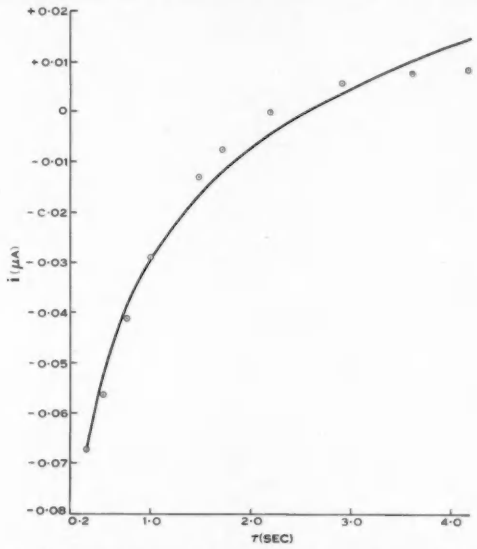

Fig. 3.—Residual current-time curve for 0·1M potassium chloride, 0·01 g/100 ml gelatin. Individual points are experimental data. The curve is for the fitted equation.

Grateful acknowledgment is made to Mr. G. G. Coote for the least-squares treatment of the data. Mr. M. C. Taylor gave valuable assistance in modifying the input of the Brush oscillograph.

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THE MAGNETIC PROPERTIES OF NITROSYL PENTAMMINE COBALT CHLORIDE*

By D. P. Mellor† and Hanneke Waterman†

Widely divergent values have been reported by different workers for the magnetic moment of cobalt in nitrosyl pentammine cobalt chloride. The values range from 1·5 Bohr magnetons (B.M.) (Ghosh and Ray 1943) to 2·8 B.M. (Ray and Bhar 1928); values lying between these extremes have been reported by Milward, Wardlaw, and Way (1938), and Mellor and Craig (1944). The variations appear to be associated with the manner in which the compound is prepared. Specimens of the complex prepared in this laboratory without paying special attention to the exclusion of air appeared to have a moment of 2·0 B.M. If, however, air is rigorously excluded during the preparation as described by Moeller and King (1953), specimens may be obtained with a molar susceptibility

Table 1

MAGNETIC MEASUREMENTS

Temp. (°K)	$10^6\chi_g$ (g)	$\mu=2\cdot839\times\sqrt{(\chi_M T)}$	Temp. (°K)	$10^6\chi_g$ (g)	$\mu=2\cdot839\times\sqrt{(\chi_M T)}$
95·5	7·82	1·26	202·3	4·30	1·39
106·1	7·32	1·28	249·8	3·63	1·43
120·1	6·63	1·30	295·5	3·12	1·46
149·5	5·70	1·36			

as low as $+765\times10^{-6}$ c.g.s. units at 23·2 °C. The moment calculated by allowing a correction of -132×10^{-6} for diamagnetism is 1·46 B.M.‡ The specimen for which this value was observed appeared under the microscope to be crystalline and homogeneous and was presumed to be pure.§ Its susceptibility increased on standing in moist air. Further measurements on the pure substance showed that its susceptibility was independent of field strength and that down to 95 °K it followed the Curie-Weiss law. The data are summarized in Table 1. Since the compound obeys the Curie-Weiss law it may be inferred that the abnormally low moment does not arise, as it does in cupric acetate, for example, from the

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‡ A similar low value has been reported by Mr. A. A. Taggart (Auckland University College, N.Z.), who has investigated a wide variety of salts of this type. He obtained a value $\mu=1\cdot39$ B.M. (susceptibility 808×10^{-6}, $T=24\cdot8$ °C) for the black chloride. This value is calculated from the formula $\mu=2\cdot839\sqrt{(\chi_M T)}$ with a diamagnetic correction of 132×10^{-6}.

§ The identity of the compound was checked by means of an analysis for cobalt (Found: Co, 24·1%. Calc. for $[Co(NH_3)_5NO]Cl_2$: Co, 24·1%).

interaction of two metal atoms. The absorption of the compound is most marked; under the microscope even thin crystals appear almost black. This suggests that the cobalt atoms may exist in two oxidation states (Co(II) and Co(III)). The moment calculated on the assumption that the compound is a dimer ($\mu = 2 \cdot 06$ B.M.) is consistent with this view of its constitution though it is difficult to see how an inner orbital d^2sp^3 bonded Co(II) complex could be formed with the ligands available (NH_3 and NO). It would seem that nothing short of a complete crystal structure analysis will clear up the constitution of this puzzling compound.

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ALKALOIDS OF THE AUSTRALIAN APOCYNACEAE: *KOPSIA LONGIFLORA* MERR.*†

II. THE IDENTITY OF KOPSAMINE

By N. G. BISSET,‡ W. D. CROW,§ and YOLANDE M. GREET||

In recent years, a number of papers has appeared on the alkaloids of *Kopsia fruticosa* (Roxb. ex Edwards) A.DC. (Bhattacharya, Chatterjee, and Bose 1949, and subsequent papers) and *K. longiflora* Merr. (Crow and Michael 1955). The former authors reported the isolation of an alkaloid kopsine ($C_{22}H_{26}O_4N_2$) for which structure I was subsequently suggested (Bhattacharya 1956), while the latter reported four alkaloids, kopsinine ($C_{21}H_{26}O_2N_2$), kopsiflorine ($C_{23}H_{28}O_5N_2$), kopsilongine ($C_{24}H_{30}O_6N_2$), and kopsamine ($C_{25}H_{30}O_7N_2$), the last two being separated only with great difficulty. As a result of further examination of kopsamine and kopsilongine it has now been shown that the two "alkaloids" previously reported were in fact not completely pure. Their separation, which will be discussed more fully in a subsequent paper, has proved extremely difficult and no large-scale method has yet been effective. Analysis of small pure samples

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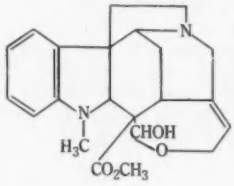
which were obtained by partition chromatography revealed that kopsamine should be reformulated as $C_{24}H_{28}O_7N_2$, while kopsilongine is $C_{24}H_{30}O_6N_2$ as previously indicated; this latter compound does not however contain a methylenedioxy group, the positive Labat test recorded being due to small amounts of admixed kopsamine.

In the recent work on *Kopsia* alkaloids, reference has been made to the paper by Greshoff (1890); the subsequent, but less accessible work of van den Driessen Mareeuw (1896) and Gorter (1920) have been overlooked. van den Driessen Mareeuw isolated an alkaloid from *K. flavida* bark, which he characterized as the bromo-compound, m.p. 286–287 °C (decomp.) and apparently regarded as



(I)

the same as that isolated by Greshoff from the seeds. The identity of this compound is not clear, as we have been unable to prepare suitable compounds for comparison. Gorter (1920) reported the isolation from the seeds of *K. flavida* Bl.* of a crystalline alkaloid, m.p. 200 °C, to which he assigned the name kopsine (cf. Bhattacharya, Chatterjee, and Bose 1949). Examination of his original sample, which was fortunately still available to us, showed that it was essentially kopsamine, and this was confirmed by purification and comparison with an authentic sample from *K. longiflora*. In order to avoid confusion it is proposed to retain the name kopsamine for this compound.

Experimental

All melting points are corrected. Microanalyses were carried out at the C.S.I.R.O. Microanalytical Laboratory at the University of Melbourne, under the direction of Dr. K. W. Zimmermann.

(*a*) *Separation of Kopsamine and Kopsilongine.*—Whatman No. 1 cellulose powder (600 g) was suspended in ethyl acetate (5 l.) and stirred vigorously while slowly adding a mixture of ethylene glycol (150 c.c.) and 5% aqueous citrate buffer (pH 3·0; 150 c.c.). The resultant slurry was packed into a chromatographic column (5·5 by 75 cm) with the aid of a perforated plunger. Crude kopsamine/kopsilongine mixture (m.p. 189–198 °C; 3·0 g) in ethyl acetate (50 c.c.) was then applied to the top of the column and elution commenced with the same solvent. Fractions of 100 c.c. were collected and analysed by paper chromatography (Whatman No. 1 paper impregnated with glycollic citrate buffer at pH 3·5 and developed with ethyl acetate).

* The species from which Gorter obtained his material is almost certainly *K. pruniformis* Reichb. f. et Zoll. ex Bakh. f. and not true *K. flavida* Bl. Because the systematics of the genus *Kopsia* and its allies are very confused and greatly in need of revision, botanical names employed in these older chemical publications must be treated with considerable reserve. This, in turn, necessitates caution in discussing the species which are reported in the literature as having been chemically investigated.

Kopsamine was eluted first, followed by a mixed band, and kopsilongine was obtained from the final fractions. Kopsamine, after several recrystallizations from acetone, was obtained as colourless prisms, m.p. 205–206 °C (corr.) (Found: C, 63·2; H, 6·2; O, 24·4; N, 5·8; CH_3O, 13·6%. Calc. for $C_{24}H_{28}O_7N_2$: C, 63·1; H, 6·2; O, 24·5; N, 6·1; $2\times CH_3O$, 13·6%), while kopsilongine was similarly obtained as colourless needles, m.p. 210–211 °C (corr.) (Found: C, 65·3; H, 6·9; O, 21·5; N, 6·4; CH_3O, 21·1%. Calc. for $C_{24}H_{30}O_6N_2$: C, 65·2; H, 6·8; O, 21·7; N, 6·4; $3\times CH_3O$, 21·0%), which failed to give the Labat test for the methylenedioxy group, and had $[\alpha]_D^{23}$ −4·2° (*c*, 2·0 in $CHCl_3$) and pK_a 6·60 in 70% methanol (previously reported $[\alpha]_D^{20}$ −18·2°; pK_a 6·80). The optical rotation of kopsamine (previously reported as $[\alpha]_D^{23}$ −46·4°) was only slightly altered ($[\alpha]_D^{20}$ −48·2° (*c*, 1·0 in $CHCl_3$)).

(*b*) *Identification of Gorter's "Kopsine".*—The base as received was a brown crystalline solid, m.p. 192–198 °C, which had obviously undergone some decomposition. Partition chromatography as described above resulted in elution of a minor constituent of high R_F closely followed by the main bulk of the alkaloid. This second fraction was recrystallized several times from acetone and obtained as colourless prisms, m.p. 204–206 °C (corr.) (Found: C, 63·1; H, 6·3; O, 24·8; N, 6·3; CH_3O, 13·9%. Calc. for $C_{24}H_{28}O_7N_2$: C, 63·1; H, 6·2; O, 24·5; N, 6·1; $2\times CH_3O$, 13·6%), undepressed by admixture with authentic kopsamine. The identity was confirmed by alkaline hydrolysis, which produced compounds identical at each stage with those produced by kopsamine (to be presented in a subsequent paper).

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